

Assessing efficacy of cardiac rehabilitation exercise therapy in heart failure patients

**Thesis submitted in accordance with the requirements
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by

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Author's Declaration

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Abstract

Background: Exercise-based cardiac rehabilitation (CR) is considered routine practice for patients following an acute cardiac event or surgical intervention. Although there is a seemingly strong evidence base supporting it for patients with chronic heart failure (CHF), provision in the UK remains poor for this patient group. In addition, data for CHF patients reported in key CR reviews and meta-analyses are not a true representation of the UKs CHF population. The transferability of current evidence into actual practice settings in the UK therefore remains incongruous.

Rationale and aims: Study outcomes have typically included an increase in VO_2 peak/ VO_2 max, a decrease in natriuretic peptides, improved left ventricular function and improved health related quality of life (QoL). Access to facilities and equipment, such as cardiopulmonary exercise testing equipment is limited in the UK for the majority of CR services thus an alternative means of assessment and exercise prescription is required. The recommended alternative for testing CHF patients is the six-minute walk test (6MWT); this requires a given space and a full practice test, the latter which adds to valuable clinical and staff time available.

Methods: The first set of studies of this thesis therefore investigated two adapted assessment procedures for use with CHF patients: i. the use of a shorter practice walk test of two minutes vs six minutes prior to a 6MWT and ii. the use of the space saving Chester step test with an adapted lower step height protocol to accommodate the anticipated lower fitness in CHF (4-inch vs 6-inch). Having determined a more practical and efficient means of assessing exercise capacity in CHF patients, this thesis then used the 6MWT to evaluate the efficacy of a typically recommended 12-week programme (for the UK) of exercise-based rehabilitation. It was the aim of this PhD to also combine the use of the Chester step test with cardiopulmonary measures as a corresponding physiological outcome in a sub-sample of participants; however due to resource problems, only validation of the low-step protocol was possible. In the main intervention study, the efficacy of a 12-week course of supervised moderate intensity exercise in CHF patients (ejection fraction <44%, NYHA class II to III) was then evaluated. For purposes of evaluating safety and recovery of any

acute myocardial stress induced by exercise in CHF, a sub-group study was performed to evaluate the influence of an acute exercise session on two-day post-exercise levels of circulating NT-proBNP.

Results: In this current suite of studies, participants were more representative of the UK CHF population than typically reported in the current evidence. Their profile involved a median age of 76 ± 16 years (mean: 67 years and range: 30 to 84 years). 98% of whom were prescribed beta-blockers, 66% were diagnosed with atrial fibrillation and 98% had two or more co-morbidities. Study 1 (Chapter 3a) verified the efficacy of a two-minute practice walk in comparison to the recommended six-minute practice walk prior to performing a baseline 6MWT in patients with CHF. Study 2 (Chapter 3b) demonstrated that a 4-inch Chester step test is a reliable assessment when space is an issue, but the criterion validity of the actual oxygen costs at each stage compared with those estimated in healthy populations were significantly lower than recommended estimations from healthy populations. Study 3 (Chapter 4) revealed individual variability in the acute response of NT-proBNP release to exercise that is worthy of further study. However the NT-proBNP data overall did not suggest a need for 'rest days' between exercise training sessions. The main intervention study (Study 4, Chapter 5) demonstrated a significant improvement in 6MWT performance responses, compared with control, where an increased walking distance of 25 m ($p < .0001$) was coupled with a reduction in heart-rate-walking speed index (T1 16.3 ± 7.3 vs T2 15.3 ± 8.7 beats per 10 walked; $p < .0001$). Perceptually, patients were walking faster for the same rating of perceived exertion (RPE 12 to 13). This improved aerobic functioning coincided with an improved NYHA class (T1 $2.3 \pm .5$ vs T2 $1.8 \pm .6$; $p < .0001$); however there was no change in resting NT-proBNP levels after 12 weeks. Patients in the "control group" who then went on to be offered the same 12-week intervention achieved similar outcomes, but delaying their commencement of an exercise programme by 12 weeks negatively impacted on participation uptake.

Key findings and conclusions: These results have demonstrated that exercise training in CHF can lead to an improvement in both physical and perceived functioning (NYHA class). In light of some previous studies showing decreases in BNP following an exercise programme and others like this one showing no change, further questions are raised about the effect of different

types and doses of activity being offered to CHF patients and the responsiveness to training of different types of patients (disease severity and demographics). The nature of the cross-over design of this study revealed that delayed commencement of exercise negatively affects participation uptake by patients, which supports current UK standards in aiming for early referral to CR.

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Glossary

ACE inhibitors Angiotensin converting enzyme inhibitors reduce peripheral vascular resistance by blocking the angiotensin converting enzyme, thereby reducing myocardial oxygen consumption which results in improved cardiac output and moderation of left ventricle hypertrophy.

Aerobic In the presence of oxygen.

Afterload The tension or stress developed in the wall of the left ventricle during ejection i.e. the end load against which the heart contracts to eject blood.

ARBs Angiotensin II receptor blockers (ARBs) are medications that block the action of angiotensin II by preventing angiotensin II from binding to angiotensin II receptors on blood vessels. As a result, blood vessels dilate and blood pressure is reduced. Reduced blood pressure makes it easier for the heart to pump blood.

Arrhythmia Any deviation from the normal heart rhythm.

Atrial fibrillation Irregular heart rhythm affecting the atria.

Beta-blocker Medication that blocks the action of adrenalin to help keep heart rate and blood pressure down.

Blood pressure The pressure exerted on the walls of the blood vessels as the heart pumps blood around the body.

Borg scale A scale used to rate perceived exertion.

Cachexia A state of malnutrition and general ill-health.

Cardiac biomarkers Measured indicators to evaluate heart function.

Cardiac output The total volume of blood pumped by the ventricles per minute; the product of stroke volume and heart rate.

Cardiomyopathy A disorder of the heart muscle of unknown aetiology.

Cardiopulmonary Exercise Testing (CPET) A non-invasive simultaneous measurement of the cardiovascular and respiratory systems during exercise to assess exercise capacity.

Chronic heart failure A condition caused by the gradual onset of the heart failing to pump enough blood around the body at the right pressure.

Chronotropic incompetence The inability of the heart to regulate its rate appropriately in response to physiologic stress.

COPD Chronic obstructive pulmonary disease, such as bronchitis.

Diastolic blood pressure The lower pressure produced by ventricular diastole (relaxation).

Dyspnoea Difficulty in breathing/shortness of breath.

Heart rate The number of ventricular beats per minute.

Heart rate reserve The difference between a person's measured or predicted maximum heart rate and resting heart rate.

Heart-rate-walking speed A ratio that can be calculated by dividing the total number of heart beats by walking distance attained during exercise testing.

Homeostasis A physiological process to maintain functions such as blood pressure and body temperature within normal limits.

ICH GCP International Conference on Harmonisation Good Clinical Practice is a quality standard.

Ischaemia Deficient blood supply to an area of the body.

Ischaemic heart disease Deficient blood supply to cardiac muscle, usually caused by atheromatous plaques.

Karvonen formula A method of calculating training heart rate.

Keteyian method A formula for calculating maximum heart rate

Left ventricular ejection fraction The proportion of the volume of blood in the ventricles at the end of diastole that is ejected during systole.

Left ventricular systolic dysfunction (LVSD) The left ventricle becomes weak and fails to efficiently pump blood around the body.

Metabolic equivalents A metabolic unit used to quantify the intensity of physical activity, which is defined as the ratio of the metabolic rate during exercise to the metabolic rate at rest. One MET corresponds to an energy expenditure of approximately 1 kcal/kg of body weight/hour, or an oxygen uptake of 3.5 ml of O₂ consumption/kg/hour.

Myocardial infarction Damage to the heart muscle usually due to a blocked coronary artery, also known as a heart attack.

Natriuresis The process of excretion of sodium in the urine via action of the kidneys.

Neurohormone A hormone secreted by a specialised neuron into the bloodstream, the cerebrospinal fluid, or the intercellular spaces of the nervous system.

NRES National Research Ethics Service supports ethical research in the NHS.

Oedema The abnormal infiltration of tissues with fluid.

Preload The end diastolic pressure that stretches the right or left ventricle of the heart i.e. the initial stretching of the cardiomyocytes prior to contraction.

Pulse pressure The difference between the systolic and diastolic pressures.

Rating of perceived exertion Interpreting sensations from the body during physical exertion.

Remodelling Changes in size, shape, structure and physiology of the heart after injury to the myocardium.

Renin-angiotensin-aldosterone system A hormone system that regulates blood pressure and fluid balance.

SNS The sympathetic nervous system. The primary process is to stimulate the body's fight-or-flight response.

Stroke volume Volume of blood ejected with each heartbeat.

Sub-maximal exercise Any physical activity whose intensity increases at regular intervals up to but never exceeding 85% of maximum heart rate.

Systolic blood pressure The higher pressure produced by ventricular systole (contraction).

Vasodilation The widening of the lumen of blood vessels.

VO₂ max Maximal oxygen consumption.

VO₂ peak Peak oxygen consumption.

Introduction

Background

Chronic Heart Failure (CHF) is a pathophysiological syndrome whereby the heart fails to pump blood at a rate proportionate to the requirements of the metabolising tissues (Shave et al., 2007). CHF patients typically present with symptoms of fatigue, exercise intolerance, oedema and dyspnoea (Rees et al., 2004). Until the late 1980s CHF was considered an absolute contraindication to exercise training (Rees et al., 2004). Common causes of CHF include previous myocardial infarction, chronic hypertension, dilated and hypertrophic cardiomyopathy, abnormalities of the heart valves and cardiac arrhythmias (Pollentier et al., 2010). CHF affects an estimated 800,000 (1.5%) people in the UK (British Society of Heart Failure, 2013). This number is expected to rise due to an ageing population and improved survival rates following myocardial infarction (British Society of Heart Failure, 2013). Poor exercise tolerance in patients with CHF has a multifactorial aetiology including: left ventricular performance, peripheral arterial and muscle metabolic-histological changes and altered neurohormonal interactions between the periphery and the heart (Giannuzzi et al., 2001). Release of natriuretic peptides is caused by increases in preload and afterload due to the compensatory actions of the sympathetic nervous system and the renin-angiotensin-aldosterone system (Conraads et al., 2004). The structural changes to the muscles and rises in circulating neurohormones is paralleled by a simultaneous increase in the degree of exercise intolerance (Gademan et al., 2007).

In addition to pharmacotherapy, exercise training is now recognised as a fundamental part of the holistic care of patients with systolic CHF (Carvalho and Mezzani, 2011; Smart, 2011), and is recommended by The European Society of Cardiology (Dickstein et al., 2008) and the National Institute for Health and Clinical Excellence (NICE) guidelines (2010). Exercise training improves the key symptoms of CHF (dyspnoea, fatigue and poor quality of life) through effects on the cardiopulmonary, vascular and musculoskeletal systems. Overall, these changes are collectively captured in an improved New York Heart Association (NYHA) classification of functional capacity (The Criteria Committee of the New York Heart Association, 1994). Furthermore exercise training has a positive influence on risk of hospitalisation, hospital re-admissions, morbidity and mortality (Normandin et al., 2013; Taylor et al., 2014).

The current evidence base is biased (see Chapter 1), as CHF patients recruited to most of the studies (typically younger males without comorbidity) underrepresent the actual population of CHF patients referred to rehabilitation in the UK CR programmes (Rees et al., 2004; Davies et al., 2010; NACR, 2013; Taylor et al., 2014; British Society for Heart Failure, 2014). In delivering exercise rehabilitation, service demands and limitations also create practical and technical challenges to the utility of assessing fitness/function and prescribing exercise in ways commensurate with that performed in most of the published evidence. Areas relevant to this thesis, where there are limitations in existing evidence leading to questions being answered in the studies to follow, include:

- a) Translation of evidence into practice in terms of demographics and co-morbidities.
- b) Technical, time and staff limitations in performing exercise assessments and interventions in 'the real world'.

Overview and rationale of thesis

In light of the limitations found in the current evidence, this thesis initially reviews the existing evidence in relation to the utility and importance of the six-minute walk test, Chester step test, plasma NT-proBNP levels, ventricular remodelling, pulse pressure, perceived QoL and the referral to and uptake of a standardised programme of exercise rehabilitation. As current UK practice of CR is challenged in reflecting the demographics, programmes and protocols found within the existing evidence base it may not be surprising that the outcomes are not as adequately achieved in clinical practice. One recent study of rehabilitation in post-MI patients (The RAMIT trial, West et al., 2012) cast doubt over the ability of UK CR programmes to reduce mortality and morbidity or to increase QoL. However, the programme protocols and the "old" data from RAMIT clearly did not meet the recommended standards and core components (BACPR, 2012; Sandercock et al., 2013; Buckley et al.; BACPR 2013).

In light of many years of personal observation and management of a heart failure rehabilitation service, corroborated by the questions raised in the literature review, the aim of this PhD was to perform a controlled study within a "real" clinically-based CR service for CHF patients. After addressing a number of underpinning technical issues around assessment parameters and

techniques, the key evaluation is presented in the final study of this thesis. The underpinning series of studies on technical issues have included four studies:

- Study 1: The validity of a time-saving 2-minute practice walk test prior to undertaking a 6-minute walk test in patients with CHF
- Study 2: The validity of a space-saving 4-inch step test in patients with CHF
- Study 3: The kinetics of NT-proBNP following a moderate intensity exercise training session (i.e. acute exercise response)

The final evaluation, Study 4, then applied the technical elements of the first four studies to evaluate the efficacy of exercise training on functionality, cardiac biomarkers, ventricular remodelling, QoL and uptake participation in a “real world” CHF rehabilitation service. Undertaken in a clinical environment, the studies have recruited patients with stable CHF, optimised on recommended CHF medication, that are representative of the clinical population in the UK (NACR, 2013).

CHAPTER 1

Review of Literature: Functionality, cardiac biomarkers and
quality of life in heart failure rehabilitation

1.1 Introduction

The existing evidence base for the efficacy of exercise training in patients with CHF demonstrates the improvements in functional capacity, natriuretic peptides, antiremodelling and QoL; there are also data which show the impact on hospital readmissions, mortality and morbidity (Piepoli et al., 2004; Davies et al., 2010; Taylor et al., 2014) as well as proving that exercise is safe (Rees et al., 2004). However, the early systematic reviews were based on small trials in patients who are not representative of the total population with CHF (Rees et al., 2004; Davies et al., 2010). It is apparent from the published research and systematic reviews that the demographic trends of the HF patients recruited into exercise training studies differ from those generally enrolled on CR exercise training programmes in the UK and in prevalence studies (British Society of Heart Failure, 2013). CHF patients participating in exercise training research tend to be younger males with few or no co-morbidities, suggesting the possibility of selection bias (Smart, 2011). This has been acknowledged by the professional bodies responsible for the production of the exercise training in HF guidelines; recognising that women, the elderly and minority groups are often excluded from clinical trials (Piepoli et al., 2011; McMurray et al., 2012). Indeed, the Heart Failure: A Controlled Trial Investigating Outcomes of Exercise (HF-ACTION) study (O'Connor et al., 2009) – the largest (2,300 patients) exercise training study of HF patients to date – confirmed that exercise plays a beneficial role in the non-pharmacological treatment of *relatively young* (mean age 59 years) patients with CHF. The Cochrane Collaboration: Exercise based rehabilitation for heart failure (Review) from 2010 (Davies et al.) questioned the transferability of the research findings to the general HF population due to the

age (mean age of 58 years) and gender (predominantly male) of the populations in the included studies. Moreover, 18 of the 20 studies included in the review cited significant co-morbidity as an exclusion criterion. The recent Cochrane Review by Taylor et al. (2014) included 33 randomised controlled trials (4740 participants) and the findings were consistent with the previous 2010 Review. Data confirmed the important benefits of exercise-based rehabilitation and there was no evidence to suggest that patients with CHF are at risk of a cardiac event during exercise training. Furthermore, a small body of evidence indicated that exercise-based rehabilitation is cost-effective. But despite clinical guidelines supporting exercise-based rehabilitation for patients with CHF, the provision and uptake remains poor in this population (Taylor et al., 2014).

Some of the key metrics and outcomes used in published studies to demonstrate the safety and efficacy of exercise training in CHF have some elements which require further evaluation, including:

- a. The value and precision of reporting the six-minute walk test (6MWT) distance alone and considerations for using other types of practical assessments (for example, step tests) for CHF populations.
- b. Levels of circulating BNP both in terms of acute responses to a single session of exercise and chronic changes over a period of training.
- c. Evidence of left ventricle remodelling
- d. The pulse pressure (PP) relationship with risk, functional capacity and related outcomes from training and
- e. Quality of life (QoL).

These questions, raised around the above elements, form the basis of this PhD, commencing with the critical review to follow.

1.2 Assessing functional capacity in chronic heart failure (CHF)

1.2.1 Introduction

CHF research studies have invariably used maximal exercise tolerance testing to measure cardiopulmonary responses (e.g. peak VO_2 and ventilator exchange ratios) from which training intensity targets and programme outcomes are assessed. This is, however, not routine clinical practice in the UK (ACPICR, 2009; BACPR 2012). Cardiac Rehabilitation (CR) practitioners adhere to professional standards and guidelines which currently recommend sub-maximal tests – in particular the 6MWT - to prescribe exercise, with the suggested heart rate training targets and training intensities being somewhat lower than those used in the reported trials (Davies et al., 2010). The validity and reliability of these sub-maximal exercise assessments to give optimum exercise prescription and physical activity advice for patients with CHF remain to be confirmed. Further questions regarding UK practice arise from the use of these sub-maximal tests in addition to the practical constraints of time, space, finance, equipment and staffing.

1.2.2 Effects of exercise training on six-minute walk distance in patients

CHF

In 1982 Butland et al. demonstrated that a six minute walk test (6MWT) could evaluate patients with chronic respiratory diseases (Faggiano et al., 2004).

Performance on the 6MWT has since become a popular and useful clinical measure of functional capacity and endurance, aimed particularly at people with moderately severe impairment (ATS, 2002; Enright, 2003), and is widely used for measuring the response to therapeutic interventions for chronic heart failure (CHF); thus 6MWD is now used as an outcome measure for CHF-rehabilitation (Guazzi et al., 2009). It is predictive of mortality and morbidity outcomes; furthermore 6MWD correlates with activities of daily living and quality of life (Enright, 2003). Individuals walking less than 300 metres in 6 minutes are at the highest risk of adverse events (Bittner et al., 1993; Haass et al., 2000; Rostagno et al., 2003) with a one-year-mortality of up to 50% (Haass et al., 2000).

Patients with CHF typically suffer exertional dyspnoea and fatigue (Pollentier et al., 2010), resulting in reduced exercise capacity (Shoemaker et al., 2012) and so the aim of exercise-based rehabilitation is to improve exercise tolerance with a corresponding reduction in symptoms. Peak oxygen consumption (peak VO_2) is reduced in patients with CHF when compared with age-matched controls due to reduced exercise cardiac output response, reduced peripheral blood flow, skeletal muscle abnormalities and metabolic abnormalities similar to those seen in severe deconditioning and as a result of these changes muscle atrophy is also common in patients with CHF (Giannuzzi et al., 2001). Breathlessness is frequently a prominent symptom during rapidly incremental protocols, and

fatigue often occurs during gradually incremented tests (Tavazzi et al., 2001). The 6MWT is considered a sub-maximal exercise test due to execution time, simplicity and greater acceptance by patients (Faggiano et al, 2004). Several studies have reported a correlation between peak VO_2 measured at maximal exercise and the 6MWD in patients with CHF (Guyatt et al., 1985; Lipkin et al., 1986; Riley et al., 1992; Cahalin et al., 1996; Roul et al., 1998; Morales et al., 1999; Zugck et al., 2000; Green et al., 2001; Opasich et al., 2001; Myers et al., 2006; Pulz et al., 2008 and Guazzi et al., 2009). The self-paced 6MWT thereby gives a more accurate representation of the ability of patients with CHF to perform sub-maximal activities of daily living (Riley et al., 1992). Statistically and clinically significant increases in 6MWD have been reported in several studies following exercise training (Table 1.1). In order to be considered as related to the intervention, the improvement in distance walked must be at least > 5% from baseline (Rostagno and Gensini, 2008); however, if the increase in distance is less than 10%, even with statistically significant results, the variation is quite possibly due to familiarisation (Opasich et al., 1998). Improvements in 6MWD ranging from 30 m (Guyatt et al., 1985) to 90 m (Spertus et al., 2005) have been associated with a significant improvement in walk performance.

Accuracy may be improved by the addition of demographic, anthropometric (height, weight, body mass index, body composition) and functional characteristics (Mandic et al. 2013).

Table 1.1 Summary of studies included in Cochrane Review (Rees et al., 2004): effects of exercise training on 6MWD

Study	Participants	Protocol	Key Findings
Tyni-Lenne R, Gordon A, Sylven C. (1996)	21 patients randomised Mean age 60 years 100% male	Endurance training 3 x per week for 8 weeks	Treatment 1: Δ 6MWD 56 m. Treatment 2: Δ 6MWD 21 m. Control: Δ 6MWD -7 m.
Tyni-Lenne R, Gordon A, Jansson E et al. (1997)	16 patients randomised Mean age 62 years 0% male	Endurance training 3 x per week for 8	The distance ambulated during 6 minutes increased 37 m ($p < 0.03$).
Gottlieb SS, Fisher ML, Freudenberger R et al. (1999)	33 patients randomised Age 64 – 67 years 88% male	Aerobic exercise 3 x per week for 6 months	6-minute walk increased by 194 ft/44.8 m ($p < 0.05$).
Owen A and Croucher L (2000)	22 patients randomised Mean age 81 years 75% male	Resistance training 1 x per week for 12 weeks	There was a significant ($p < 0.012$) improvement in 6MWD amounting to approximately 20%.
Pu CT, Johnson MT, Forman DE et al. (2001)	16 patients randomised Mean age 77 years 0% male	Resistance training 3 x per week for 10 weeks	6MWD increased by 49 ± 14 m (13%) in the intervention group.
Tyni-Lenne R, Dencker K, Gordon A et al. (2001)	24 patients randomised Mean age 63 years 54% male	Resistance exercise training 3 x per week for 8 weeks	The distance walked during the 6MWT increased in the intervention group from 500 ± 64 m to 555 ± 59 m ($p < 0.002$).

Study	Participants	Protocol	Key Findings
McKelvie RS, Teo KK, Roberts R et al. (2002)	181 patients randomised Mean age 66 years 81% male	Aerobic and resistance exercise 2 x per week for 3	There was a significant increase in 6MWD compared with baseline at 3 months ($p < 0.01$) for both exercise ($+22 \pm 5$ m) and control ($+15 \pm 5$ m) groups. A significant increase in 6MWD compared with baseline at 12 months ($p < 0.05$) was found for both exercise ($+17 \pm 8$ m) and control ($+20 \pm 9$ m) groups.
Parnell MM, Holst DP, Kaye DM et al. (2002)	21 patients randomised Age 53 – 57 years 91% male	Aerobic exercise 5 – 7 x per week for 8 weeks	Exercise training significantly increased 6MWD (474 ± 27 to 547 ± 34 m; $p = 0.008$).

1.2.3 Reproducibility and validity of the six-minute walk test (Table 1.2)

In 1985 Guyatt et al. first validated the 6MWT for use with CHF patients and also reported the effects of encouragement on walking performance. Subjects undertook a maximal cycle ergometer test and a 6MWT was administered six times over a 12-week period. Their study of 18 patients with CHF and 25 patients with chronic lung disease showed that reproducible results were achieved after the first two walks and that encouragement significantly improved walk test performance ($p = 0.02$); thus demonstrating that results of a 6MWT are reproducible when a standardised protocol is followed. A systematic review by Pollentier et al in 2010 extracted data from 14 trials to examine the ability of the 6MWT in determining functional capacity in patients with CHF. The authors reported on reproducibility of the 6MWT using data from 9/14 trials, validity from 12/14 and predictive value of the 6MWT from 5/14. Sample size ranged from 14 to 63 participants in the majority of trials, with 3 reporting sample sizes > 100 participants. Many used maximal exercise testing in order to assess VO_2 max: 7/14 used a cycle ergometer, 6/14 used a treadmill and the shuttle-walk test was also used in several studies. One study that was included in the review examined the reproducibility and responsiveness to change of a 6MWT and a quality of life measure specifically in elderly patients with CHF (O'Keefe et al., 1998). The authors recruited 60 elderly patients with a mean age 82 years, and patients completed a 6MWT at baseline and at 3 to 8 weeks. An intraclass correlation coefficient (ICC) of 0.91 was reported for 24 patients with no change in cardiac status at review. In a large trial, involving over 1000 patients over the age of 60 years, Ingle et al. (2005) examined 1-year reproducibility of the 6MWT, the sensitivity to self-perceived changes in symptoms of CHF and

patient numbers required for studies using the 6MWT. They used a questionnaire to assess CHF symptoms, and patients performed a baseline 6MWT, with follow-up at 1 year. Seventy four patients who reported unchanged symptoms also had an unchanged 6MWD, with an ICC of 0.80. There was a negative correlation between change in symptoms and change in 6MWD ($r = -0.55$; $p = 0.0001$) in 423 patients who reported an improvement in symptoms, and a moderate inverse correlation ($r = -0.53$; $p = 0.0001$) in 516 patients who reported a deterioration of symptoms. For all patients, regardless of symptom status, a high inverse correlation ($r = -0.75$; $p = 0.0001$) was observed. The use of questionnaires in the studies by O'Keefe et al. (1998) and Ingle et al. (2005) could present bias due to their subjective nature. Nonetheless, the 6MWT did demonstrate reasonable reproducibility and responsiveness in elderly patients with CHF and change in 6MWD appeared to be sensitive to change in self-perceived symptoms of CHF. However, Buckley (2011) has since demonstrated that the combined use of an ICC and Bland and Altman's (1986) bias \pm 95% limits of agreement (95%LoA) analysis concurrently highlight clinical and statistical significance and thereby confirm reliability, which is crucial in populations with a low functional capacity such as CHF patients.

Table 1.2 Reproducibility and validity of the 6MWT

Study	Participants	Protocol	Key Findings
Guyatt, Sullivan, Thompson et al. (1985)	18 patients with CHF 25 patients with chronic lung disease 34 male, 9 female Mean age 64.7 ± 8.3 years	6MWT administered six times over 12 weeks (2-week intervals)	Encouragement improved walk test performance ($p < 0.02$). Improvement in walk distance seen up to the third walk.
Lipkin, Scriven, Crake, Poole-Wilson. (1986)	26 patients with stable CHF Mean age 58 years NYHA II to III	Maximal treadmill test to determine oxygen consumption and 6MWT	Relation between maximum oxygen consumption and 6MWD was curvilinear. In patients with low maximum oxygen consumption 6MWD varied considerably. In patients with high maximum oxygen consumption and normal subjects 6MWD varied very little.
Riley, McParland, Stanford, Nicholls. (1992)	16 patients with CHF Mean age 65.2 years NYHA II to IV 14 male, 2 female	Maximal treadmill test to determine VO_2 . 3 x 6MWT with VO_2 measured	6MWD correlated with peak VO_2 as measured during treadmill test ($r = 0.88$; $p < 0.001$). 6MWT good reproducibility (coefficient of variation = 6.71).
Faggiano, D'Aloia, Gualeni et al. (1997)	26 patients with mild to severe heart failure 24 male, 2 female Mean age 56 ± 11 years NYHA II to IV	Symptom-limited cycle ergometer test. 6MWT. VO_2 also measured during 6MWT	Peak VO_2 during cycle test 15 ± 4 ml/kg/min; during 6MWT 12.9 ± 4.4 ml/kg/min ($p < 0.05$).

Study	Participants	Protocol	Key Findings
Roul, Germain, Bareiss. (1998)	121 patients with CHF Mean age 59 ± 11 years	Symptom-limited cycle ergometer test. 6MWT x 2 in 40 of the 121 patients	Peak VO_2 group 1 = 18.5 ± 4 vs group 2 = 13.9 ± 4 ml/kg/min ($p = 0.0001$). In patients who walked < 300m there was a significant correlation between distance and peak VO_2 ($r = 0.65$; $p = 0.011$).
O'Keefe, Lye, Donnellan, Carmichael. (1998)	60 elderly patients with CHF Mean age 82 years 22 male, 38 female NYHA I to IV	Standardised 6MWT. CHF questionnaire (CHQ). Repeated in 45 patients at 3 to 8 weeks	6MWT demonstrated good reproducibility (ICC 0.91) in the 24 patients who, at review, reported no change in cardiac status. Good correlation at baseline between 6MWD and CHQ score ($r = 0.79$).
Zugck, Krüger, Dürr et al. (2000)	113 patients with stable CHF Mean age 54 ± 12 years NYHA class 2.2 ± 0.8	Symptom-limited cycle ergometer test. 6MWT repeated in 10 patients on 3 consecutive days	Moderate correlation between 6MWD and peak VO_2 ($r = 0.69$ in males, $r = 0.59$ in females; $p = 0.001$).
Demers, McKelvie, Negassa, Yusuf. (2001)	768 patients enrolled in the RESOLVD pilot study	6MWT performed once at screening and twice at baseline, 18 weeks and 43 weeks	ICC 0.90 at baseline, 0.88 at 18 weeks, 0.91 at 43 weeks. Baseline 6MWD moderately inversely correlated to NYHA class ($r = -0.43$; $p = 0.001$).
Ingle, Shelton, Rigby et al. (2005)	1077 patients with CHF > 60 years NYHA class > II	Questionnaire and baseline 6MWT. 1-year follow-up	74 patients with unchanged symptoms had unchanged 6MWD (ICC 0.80).

Study	Participants	Protocol	Key Findings
Guimarães, Carvalho, Bocchi. (2008)	23 males with CHF Mean age 50 ± 9 years NYHA class II to III	Treadmill 6MWT guided by Borg scale (RPE 11 – 13). Repeated. VO ₂ measured during 6 th minute	ICC at minute 6: VO ₂ $r = 0.92$, $p < 0.0001$; RQ < 1 $r = 0.60$, $p = 0.004$. 6MWD highly reproducible between the 2 tests (0.20 ± 0.03 vs 0.20 ± 0.04 miles or 321 metres; $r = 0.88$, $p < 0.0001$).
Guazzi, Dickstein, Vicenzi, Ross. (2009)	253 patients with systolic (n = 211) or diastolic (n = 42) heart failure Mean age 61.9 ± 10 years NYHA class 2.2 ± 0.78	2 x 6MWT on separate days. Symptom-limited cycle ergometer test.	6MWD correlated with CPET variables. No significant difference in distance walked between survivors and non survivors (353.2 ± 95.8 vs 338.5 ± 76.4 m; $p = \text{NS}$). 6MWD not associated with survival.

Table 1.3 Studies presenting concurrent changes in exercise-based controlled trial outcomes from the systematic review by Shoemaker et al. (2012)

Author	Participants	6MWT	Peak VO ₂	QoL	Summary	Included in the Cochrane Review 2004/2014	
Tyni-Lenne et al. (1996)	Intervention 1 n = 7 Intervention 2 n = 7 Control n = 7	√	√	√	Intervention1: Δ6MWD 56 m Intervention 2: Δ6MWD 21 m Control: Δ6MWD -7 m	√	
Tyni-Lenne et al. (1997)	Intervention n = 8 Control n = 8	√	√		Intervention: Δ6MWD 37 m Control: Δ6MWD -2 m	√	
Gottlieb et al. (1999)	Intervention n = 11 Control n = 14	√	√	√	Intervention: Δ6MWD 44.8(59.1) m Control: Δ6MWD -18.6(40.8) m	√	√
Tyni-Lenne et al. (2001)	Intervention n = 16 Control n = 8	√	√		Intervention: Δ6MWD 55 m Control: Δ6MWD 0 m	√	
Pu et al. (2001)	Intervention n = 9 Control n = 7	√	√		Intervention: Δ6MWD 49 m Control: Δ6MWD -3 m	√	
McKelvie et al. (2002)	Intervention n = 90 Control n = 91	√		√	Intervention: Δ6MWD 22(47) m Control: Δ6MWD 15(48) m	√	√
Parnell et al. (2002)	Intervention n = 11 Control n = 10	√		√	Intervention: Δ6MWD 73 m Control: Δ6MWD -2 m	√	
Van den Berg-Emons et al. (2004)	Intervention n = 18 Control n = 16	√	√	√	Intervention: Δ6MWD 46 m Control: Δ6MWD 13 m		
Corvera-Tindel et al. (2004)	Intervention n = 42 Control n = 37	√	√	√	Intervention: Δ6MWD 36 m Control: Δ6MWD -3 m		
Gary et al. (2004)	Intervention n = 32 Control n = 32	√		√	Intervention: Δ6MWD 62 m Control: Δ6MWD 28 m		

Authors	Participants	6MWT	Peak VO ₂	QoL	Summary	Included in the Cochrane Review 2004/2014	
Yeh et al. (2004)	Intervention n = 15 Control n = 15	√	√	√	Intervention: Δ6MWD 85 m Control: Δ6MWD -51 m		
Witham et al. (2005)	Intervention n = 41 Control n = 41	√		√	Intervention: Δ6MWD 1 m Control: Δ6MWD 6 m		√
Austin et al. (2005)	Intervention n = 100 Control n = 100	√		√	Intervention: Δ6MWD 44 m Control: Δ6MWD -6 m		√
Jonsdottir et al. (2006)	Intervention n = 21 Control n = 22	√	√		Intervention: Δ6MWD 37 m Control: Δ6MWD 6 m		√
Brubaker et al. (2009)	Intervention n = 30 Control n = 29	√	√	√	Intervention: Δ6MWD 56 m Control: Δ6MWD 47 m		
Davidson et al. (2010)	Intervention n = 53 Control n = 52	√		√	Intervention: Δ6MWD 82 m Control: Δ6MWD 24 m		√
Kitzman et al. (2010)	Intervention n = 26 Control n = 27	√	√	√	Intervention: Δ6MWD 51 m Control: Δ6MWD 15 m		
Gary et al. (2010)	Intervention n = 17 Control n = 18	√		√	Intervention: Δ6MWD 38 m Control: Δ6MWD -60 m		√

Table 1.4 Summary of 2MWT studies

Study	Participants	Diagnosis	Protocol	Key Findings
Butland, Pang, Gross et al. (1982)	Study 1: 10 patients Study 2: 30 patients Study 3: 13 patients	Chronic airflow obstruction due to chronic respiratory disease	Study 1: Pacing during 12-minute test Study 2: Comparison of two-, six- and 12-minute tests Study 3: Reproducibility of two-minute test Repeated	Study 1: Patients walked further during first two minutes. Study 2: the three tests were highly correlated.
Upton, Tyrrell and Hiller (1988)	Group1: 32 female, 57 male healthy children Group 2: 27 female, 23 male children with Cystic Fibrosis	Cystic Fibrosis	Evaluation of two-minute walk distance as an objective measure of exercise tolerance Repeated	Group 1: significant improvement on second test ($p < 0.01$). Group 2: no significant difference between first and second walks.
Brooks, Parsons, Hunter et al. (2001)	290 patients	Unilateral transtibial, unilateral transfemoral or bilateral amputations	Validity and responsiveness of a 2MWT in individuals with lower extremity amputation Repeated	Significant improvement in two-minute walk distance at discharge and follow up compared with baseline (increase of $13.6 \pm 19.9\text{m}$ at discharge, at follow up $41.2 \pm 34\text{m}$; $p < 0.001$).

Study	Participants	Diagnosis	Protocol	Key Findings
Brooks, Parsons, Jeng et al. (2004)	122 patients	Cardiac surgery (CABG)	Validity and sensitivity of the 2MWT Repeated	Two-minute walk distance reduced post operatively from $138 \pm 26\text{m}$ to $84 \pm 33\text{m}$ ($p < 0.001$), but increased again at follow up to $151 \pm 31\text{m}$ ($p < 0.0001$).
Kosak and Smith (2005)	12 female, 6 male patients	Stroke	Reliability and sensitivity to change of two-, six- and 12-minute walk test Repeated	ICCs for two- and six-minute walk tests 0.85 and 0.78 respectively ($p < 0.0007$). Correlations for 2- and 6-minute walk tests were $r = 0.997$ 6MWD overestimated based on two minute assessment.
Leung, Keung, Chan et al. (2006)	8 female, 37 male patients	COPD	Reliability, validity and responsiveness of a 2MWT in patients with moderate to severe COPD.	High test-retest reliability for 2MWT. Significant correlations between 2MWT and 6MWT. 2MWT is a reliable and valid test for assessment of responsiveness following rehab in COPD.

1.2.4 Changes in 6MWT distance following training in CHF patients

Statistically and clinically significant increases in 6MWD have been reported in several studies following exercise training. The first Cochrane Review of exercise based rehabilitation for heart failure by Rees et al. in 2004 (Table 1.1) and an update by Davies et al. in 2010 reported a weighted mean difference for the exercise intervention versus usual care of 41 m (95% CI -64.65 – 17.10). However, this distance only accounts for the differences between the intervention and the control groups. The degree of change that is considered to be clinically meaningful has not been well studied, and as stated above this could be anything from 30 m (Guyatt et al., 1985) to 90 m (Spertus et al., 2005). In addition, familiarisation with the test can influence final outcome tests, hence the need for a practice test. Analysis of change in the 6MWD and simultaneous change in other outcome measures would test the responsiveness of the 6MWT as a study endpoint more rigorously. In a review to determine the amount of change in the 6MWD (Δ 6MWD) that was clinically meaningful in CHF patients, Shoemaker et al. (2012) analysed data from 13 studies reporting the ICC of the 6MWT, and 18 studies using the 6MWT along with either aerobic capacity and/or quality of life (QoL). They used a novel approach for triangulating the Δ 6MWD that should be regarded as clinically meaningful and concluded that a Δ 6MWD of approximately 45 m exceeded measurement error and was associated with significant changes in either aerobic capacity and/or QoL (Table 1.3). It is worth noting that studies examining 6MWD as an outcome measure have not reported changes in other measures of functional capacity. In patients with poor exercise capacity the 6MWD alone may not be sensitive enough to increases in functional capacity. It may be beneficial for CR programmes to

examine differences in heart rate, for example, in combination with changes in 6MWD (Buckley et al., 2010) and as such, this was examined further in Study 4 (Chapter 5).

1.2.5 Practice test of 6MWT

Both in clinical practice and in research when using the 6MWT in CHF, a practice test is recommended to increase the reliability of the test by filtering out the influences of familiarisation on final outcome tests, as discussed in above (Opasich et al., 1998). Current recommendations suggest that patients need to perform a full practice test, but there is concern that this may induce significant fatigue and the need for rest stops. Patients with severe CHF may become exhausted after only a few minutes of exercise testing, therefore actual exercise capacity may be underestimated (Leung et al., 2006). The two-minute walk test (2MWT) was first proposed by Butland et al. in 1982 and was reported as being a valid test in COPD patients (no p value reported); its validity and responsiveness were later confirmed as further studies (Table 1.4) have shown that a 2MWT is a reliable, valid and sensitive test for the assessment of exercise capacity in patients with moderate to severe COPD (Leung et al., 2006), neurologic impairment (Rossier and Wade, 2001), stroke (Kosak and Smith, 2005) and cardiac surgery (Brooks et al., 2004). The two-minute walk distance correlates well with longer walk tests (Butland et al., 1982; Upton et al., 1988; Kosak and Smith, 2005; Leung et al., 2006). Interestingly, Leung et al. (2006) found small but significant differences in the end of test RPEs between 2MWT and 6MWT in their study of 45 patients with COPD, indicating that the 6MWT was more exhausting to perform than the 2MWT. Thus, pacing may be

different in a 2MWT compared with a 6MWT, as a patient who knew that a test was only going to last two minutes would probably walk faster and therefore further than a patient would walk in the first two minutes of a longer test. Furthermore, 6MWD is significantly overestimated based on the two minute walk distance (2MWD), possibly due to fatigue (Kosak and Smith, 2005); nonetheless, the 2MWT is considered a valid and time-efficient measure of self-paced walking speed, less hampered by fatigue than longer walking tests.

In conclusion the 6MWT is a simple test, requiring very little equipment. The test does, however, require considerable space, unlike the Chester step test (CST) which is an alternative test often adapted for use in CR. The CST has not yet been validated for use with CHF patients, however, and this was assessed further in Study 2 (Chapter 3b). The 6MWT shows good test-retest reliability across the literature particularly when a standardised protocol is used. The results, however, are not valid until after the first trial due to the learning effect of the test (Riley et al., 1992; Morales et al., 1999); hence the need for a practice test. However, this can prove time consuming within the restrictions of clinical time available for CR teams. The use of a two-minute practice test was questioned in Study 1 (Chapter 3a). The correlation of the 6MWT to peak VO_2 is good; with a 6MWD < 450 to 490 m the 6MWT is between 83% and 91% accurate, respectively, in predicting peak VO_2 (Pollentier et al., 2010). Furthermore, stronger correlations are observed in advanced CHF where patients have a reported 6MWD < 300 m or a VO_2 < 10 ml/kg/min. As the 6MWT is time limited it is difficult to predict VO_2 in patients who are fitter and

therefore have a higher VO_2 max; thus the 6MWT is less accurate in predicting peak VO_2 in patients who have a 6MWD > 490 m (Pollentier et al., 2010).

1.3 Effects of acute moderate-intensity exercise on B-type natriuretic peptides in patients with CHF

1.3.1 Introduction

Cardiac biomarkers are used in the diagnosis and risk stratification of patients with CHF (Kociol et al., 2010). Not only are biomarkers useful clinical tools, they often provide insight into the underlying pathophysiology. For example, evolving evidence suggests that CHF patients have increased levels of cardiac troponins (cTn) – biomarkers for myocardial injury. Levels are more marked in patients with advanced disease and decompensated HF, and these increased levels are associated with poor outcomes (Kociol et al., 2010). Several mechanisms for cTn release have been proposed but it is not yet clear whether myocardial injury is a cause or effect of decompensation.

Plasma atrial natriuretic peptide (ANP) and brain or B-type natriuretic peptide (BNP) levels increase in patients with HF commensurate with the deterioration of clinical symptoms and haemodynamics; consequently, assays for these peptides are useful in the diagnosis and follow-up of cardiac patients (Clerico et al., 1998; Koglin et al., 2001). ANP is released from the atria and ventricles in response predominantly to atrial wall stress and stretch, leading to vasodilation and natriuresis. Together ANP and BNP form an integrated natriuretic peptide system with important compensatory (cardiovascular, renal and endocrinologic)

actions in patients with HF (Bonow, 1996). However, BNP is considered superior to ANP for distinction between normal subjects and patients with various degrees of HF (Cowie et al., 1997; Clerico et al., 1998). Being an antagonist of the renin-angiotensin-aldosterone system, brain or B-type natriuretic peptide (BNP) levels are raised due to pathologic (chronic heart failure) or physiologic (exercise) stimuli due to ventricular myocyte stretch resulting from increased central blood volume. The function of BNP is to reduce myocardial wall stress (Scharhag et al., 2008) in order to maintain homeostasis (Shave et al., 2007). It achieves this by increasing vasodilation (reduces afterload) as well as being sympathoinhibitory and diuretic (reduces preload). The increase in BNP release consequent to endurance and/or strength training in healthy sedentary individuals is well known (Scharhag et al., 2008). These increases are short-term and are thought to be due to the physiologic stimulus of exercise (Shave et al., 2007) and not pathological in nature; in fact Scharhag et al. (2008) suggest that they may have cytoprotective and growth-regulating effects on the athletes' heart.

1.3.2 Changes in BNP levels following acute exercise

Exercise is known to stimulate secretion of atrial natriuretic peptide (ANP) levels in patients with CHF due to increases in atrial pressure and wall stretch (Kato et al., 2000). Despite this, the effect of exercise on plasma BNP levels in CHF patients has received less attention. There are apparent differences in the tissue specific expression and production of ANP and BNP, and in the mode of release (Friedl et al., 1999). The release of BNP appears to be directly proportional to ventricular volume expansion and caused by a pressure-related

release mechanism (Steele et al., 1997; Kato et al., 2000). Unlike ANP, which is contained in storage granules, BNP is synthesised in bursts (McNairy et al., 2002) and is under constant renewal following production by the transcription and translation of messenger RNA (Shave et al., 2007). The half-life of BNP in plasma is 5 to 10 times longer than for ANP, which is cleared almost immediately thus BNP may not be subject to rapid changes. BNP has a half-life of approximately 20 minutes, and NT-proBNP has a half-life of 1 to 2 hours (Januzzi, 2006). The synthesis of BNP is considered to be regulated at a constant rate which would suggest that exercise of a short duration might not be sufficient to increase BNP secretion and thereby result in an increase in plasma levels (Kato et al., 2000). Koglin et al. (2001) examined the role of BNP in risk stratifying patients with CHF, which indicated that any observed increase in BNP of < 100 ng/l (or pg/ml) would signify that patients remain stable. A few studies involving vigorous exercise (Table 1.5) have reported increased plasma BNP levels in relatively young CHF patients (48 years to 62 years, and one study median age 66 years). These changes were associated with both left ventricular systolic dysfunction (LVSD) and diastolic dysfunction (Matsumoto et al., 1995; Steele et al., 1997; Kato et al., 2000; Mottram et al., 2004).

Matsumoto et al. (1995) reported an increase of 157 ± 79 pg/ml in 7 patients with dilated cardiomyopathy (DCM), which was significantly larger than the increment seen in 9 patients with mitral stenosis ($+17 \pm 5$ pg/ml, $p < .05$). Similarly, Steele et al. (1997) and Kato et al. (2000) reported that BNP levels increased significantly at peak exercise when compared with resting levels in their CHF groups. Interestingly, Steele et al. (1997) found that there was a significant reduction in LVEF from rest to peak exercise only in the control group

($p < .001$), but the measurements did not relate to exercise performance. This suggests that changes in LVEF do not contribute to the increase in BNP levels as there would also have been an anticipated rise in BNP levels in the control group at peak exercise. The authors attributed this lower LVEF to the age of the subjects (65 – 69 years). In 2004, Mottram et al. recruited 26 patients with suspected diastolic heart failure (DHF). BNP increased with exercise from 48 ± 57 to 74 ± 97 pg/ml ($p = .007$) and was higher in patients with elevated filling pressures at peak exercise. Though this increase was statistically significant it was not of clinical significance (Koglin et al., 2001). Patients with DHF had higher diastolic pressure at any given cardiac volume: there was a preserved end-systolic pressure-volume relationship but an abnormal diastolic relationship, which suggests that a pressure-related release mechanism is responsible for the observed increases in BNP levels (Steele et al., 1997; Kato et al., 2000).

In contrast to the above, Friedl et al. (1999), McNairy et al. (2002) and Krüger et al. (2004) reported that BNP levels do not increase with exercise (Table 1.5). Friedl et al (1999) assessed 16 patients with LVSD using a supine ergometric maximal stress test, where BNP levels were measured 3 minutes post exercise, with no significant increases (86 ng/l to 104 ng/l; +18 ng/l). McNairy et al. (2002) assessed 30 CHF patients (10 NYHA class I or II, 10 patients NYHA class III or IV and 10 controls), where BNP was assessed at rest and immediately after exercise on a cycle ergometer at 75% of maximum heart rate. BNP levels increased by 55% in the control group (with values remaining within normal limits), by 30% in the NYHA I-II group from 126 pg/ml to 164 pg/ml (+38 pg/ml) and in the NYHA III-IV group from 1712 pg/ml to 2019 pg/ml. Although the

increase of 18% (+307pg/ml) in the NYHA III-IV group was not statistically significant, this increase would be considered significant clinically (Koglin et al., 2001). Unlike other studies a further BNP measurement was performed one hour after exercise, with levels returning to within 5% of baseline. Krüger et al. (2004) similarly concluded that, in 37 patients with CHF, BNP could be safely used in an outpatient setting to accurately diagnose CHF without fear of a false-positive result caused by exercise prior to testing, stating that significant changes in BNP levels in patients with CHF reflected changes in their clinical status and did not result from physical activity even when exercised to anaerobic threshold. Interestingly, in six of the 37 patients BNP levels decreased following exercise. A similar finding was reported only in one previous abstract by Lainchbury et al. (2001). Recently Normandin et al. (2013) compared high-intensity interval exercise with moderate-intensity continuous exercise and measured BNP levels before and at 20 minutes and 24 hours after exercise. In neither of these exercise training protocols nor at these two time points were there any increases in BNP.

The studies referred to above have examined BNP responses only as far as 24 hours post acute exercise. Despite the half-life, this may not be a sufficient duration in pathological populations, especially moving beyond 24 hours post exercise where the longer term effects of acute exercise could be determined. CR standards and guidelines recommend that patients attend supervised exercise sessions at least twice per week, but there is no supporting evidence regarding the number of days there should be between sessions and knowledge of changes in BNP data would provide novel insight into the short

and long term stress placed on the cardiovascular system by rehabilitation exercise and thus add to the debate about adequate recovery between sessions. Changes in NT-proBNP levels in patients with CHF immediately after and up to 72 hours following moderate intensity exercise were examined in Study 3 (Chapter 4).

Table 1.5 Summary of studies investigating acute BNP response following exercise in CHF

Study	Participants	Protocol	Key Findings
Responders			
Matsumoto A, Hirata Y, Momomura S et al. (1995)	7 patients with dilated cardiomyopathy (6 male) Baseline BNP 221 ± 80 pg/ml	Symptom-limited cycle ergometer. BNP sample at rest and at peak exercise. Medication stopped 24 hours prior to study.	BNP increased > 100 pg/ml from 221 ± 80 pg/ml at rest to 378 ± 115 pg/ml at peak exercise; $p < 0.01$). Limitations: small numbers recruited, mean age very young and not representative of CHF population. Effects of stopping medication prior to testing unknown.
Steele IC, McDowell G, Moore A et al. (1997)	10 patients with compensated CHF 10 normal controls Baseline BNP 42 pg/ml	Symptom-limited cycle ergometer. BNP sample at rest, at peak exercise and at 3 and 6 minutes of recovery. Medication not taken on day of testing.	Significant rise in BNP at peak exercise compared with resting level in patients with CHF (42 pg/ml to 46 pg/ml; $p < 0.001$) but no change in control group. At rest and at peak exercise BNP significantly negatively correlated with LVEF ($p < 0.0001$). Limitations: small number of patients recruited. Effects of stopping medication prior to testing unknown. Mean baseline BNP is low compared to other studies.
Kato M, Kinugawa T, Ogino K et al. (2000)	29 patients with LVD 32 patients with CHF LVD group baseline BNP 124 ± 28 pg/ml CHF group baseline 268 ± 38 pg/ml	Symptom-limited cycle ergometer. BNP sample at rest and at peak exercise.	BNP levels increased significantly post exercise in all groups. Patients with CHF had progressively higher BNP exercise ratio, demonstrating that the augmented exercise BNP response exists early in the course of developing CHF.

Study	Participants	Protocol	Key Findings
Mottram PM, Haluska BA, Marwick TH (2004)	26 patients with hypertension and suspected DHF Baseline BNP levels not reported; however graph shows all baseline values < 1000 pg/ml	Symptom-limited treadmill ETT (Bruce protocol). BNP sample at rest and within 1 minute of peak exercise. Medication not withheld.	BNP increased with exercise from 48 ± 57 to 74 ± 97 pg/ml; $p = 0.001$. Peak exercise BNP was higher in patients with elevated filling pressures at peak exercise ($p = 0.027$). Limitations: unclear as to whether results of this study are transferable to general CHF population, including those with systolic dysfunction.
Non-responders			
Friedl et al. (1999)	16 patients with CHF Normal, age-matched controls Baseline BNP in CHF group 86 ng/l	Symptom-limited supine cycle ergometer. Medication stopped 12 hours prior to testing.	BNP activity increased with exercise; however the increase was statistically not significant. Limitations: small number of patients recruited. Effects of stopping medication prior to testing unknown.
McNairy M, Gardetto N, Clopton P et al. (2002)	10 patients NYHA class I – II, 10 patients NYHA class III – IV 10 healthy subjects NYHA I/II group baseline 126 ± 26 pg/ml NYHA III/IV group baseline 1712 ± 356 pg/ml	Cycle ergometer to 75% of calculated MHR. BNP sample at rest, immediately after and 1 hour after completion of exercise test. Medication stopped on the day of testing.	55% increase from baseline in BNP level (29 to 45pg/ml) in control group. 30% increase in BNP level (126 to 164 pg/ml) in NYHA I – II group. 18% increase in BNP level (1712 to 2019 pg/ml) in NYHA III – IV group (an increase > 100 pg/ml). One hour after exercise BNP levels had returned to within 5% of baseline.

Study	Participants	Protocol	Key Findings
<p>Krüger S, Graf J, Merx MW et al. (2004)</p>	<p>37 patients with CHF</p> <p>Baseline BNP in patients with an observed increase 447 ± 432 pg/ml (mean age 57 years)</p> <p>Baseline BNP in patients with an observed decrease 294 ± 369 pg/ml (mean age 71 years)</p>	<p>Symptom-limited cycle ergometer.</p> <p>BNP sample at rest, at peak exercise and at 1 and 5 minutes of recovery time.</p> <p>Assumed medication not stopped.</p>	<p>No significant change during exercise in control group.</p> <p>No significant change during exercise in CHF group, although levels increased in 84% of CHF patients and decreased in 16% compared to resting levels.</p> <p>Limitations: not reported whether medication was withheld prior to testing.</p>
<p>Normandin E, Nigam A, Meyer P et al. (2013)</p>	<p>20 patients with CHF and reduced LVEF</p> <p>Baseline levels not reported</p>	<p>Patients performed 1 session of high intensity interval exercise and 1 of moderate intensity continuous exercise.</p> <p>BNP measured before exercise and 20 minutes and 24 hours after an exercise session.</p> <p>Assumed medication not stopped.</p>	<p>No significant increase in BNP seen at 20 minutes and 24 hours post HIIE and post MICE.</p> <p>Limitations: not reported whether medication was withheld prior to testing.</p>

1.4 Effects of exercise training on B-type natriuretic peptides in patients with CHF

1.4.1 Introduction

The specific use of BNP (a biomarker of myocardial dysfunction) testing is recommended in the current National Institute for Health and Clinical Excellence (NICE) Guidelines for Chronic Heart Failure (2010) and in the European Society of Cardiology Guidelines (Dickstein et al., 2008). BNP is a neurohormone released predominantly from ventricular myocytes in response to increased stretch (Shave et al., 2007) and pressure overload (Smart et al., 2011). It is also produced by cardiofibroblasts to elicit its anti-fibrotic effects in the heart (Mangiafico et al., 2013). BNP is produced and released as a 108 amino acid prohormone in a glycosylated form (pre-pro-BNP), which is gradually deglycosylated (cleaved) in the circulation into biologically active BNP and into inactive N-terminal (NT)-proBNP. NT-proBNP appears to be more stable than BNP (i.e. a larger half-life); hence it's preferred use as an outcome measure in many studies (Smart and Steele, 2010). In stable ischaemic heart disease (IHD), BNP and NT-proBNP have proven accuracy and near identical test performance in ruling out severely reduced left ventricular ejection fraction (LVEF), prediction of all-cause mortality or HF regardless of the effects of age, gender and renal function - all factors known to affect BNP levels (Richards et al., 2006).

BNP has powerful systemic cardiovascular actions, including a reduction in cardiac output and filling pressures which result from vasodilation and

decreased venous return. As an antagonist of the renin-angiotensin-aldosterone system, the biological properties of BNP include natriuresis and sympathoinhibitory effects as well as vasodilation (Scharhag et al., 2008; Mangiafico et al., 2013). It has been suggested that the levels of natriuretic peptides denote the severity of heart failure and also reflect the body's attempt to compensate and maintain homeostasis (Koglin et al., 2001). Adverse effects of increased BNP release may be reduced skeletal blood flow, cachexia, left ventricle and vascular remodelling, depression of cardiac contractility, oxidative stress, vasoconstriction and endothelial cell apoptosis (Anker and Von Haehling, 2004).

CHF is also accompanied by an increase in other neurohormonal markers, such as noradrenaline/norepinephrine, renin, aldosterone, endothelin and arginine vasopressin) but evaluation of these markers is not considered of use for diagnostic or prognostic purposes, although they are of interest in research studies (ECS, 2008).

1.4.2 Changes in BNP levels following exercise training in CHF patients

As mentioned above, it was initially thought that the heart increases production and release of BNP during CHF as a compensatory mechanism in response to increased water retention and cardiac stress; indeed increasing levels of BNP have been associated with poor mortality and morbidity. However, Mangiafico et al. (2013) reported that recent studies using more sensitive technologies demonstrated that, in patients with CHF and high plasma BNP levels assessed by conventional assays, there was a lack of mature BNP in its active form.

Thus, despite the elevated levels of BNP seen in advanced CHF, sensitive mass-spectrometry indicated that less biologically active precursors and multiple degraded forms of BNP were actually present. This suggests that altered processing of BNP occurs in patients with CHF, resulting in a deficiency of the active hormone and thereby it's compensatory and protective properties. Nonetheless, measurements of both BNP and NT-proBNP continue to be valuable in the diagnosis of suspected acute or CHF (Januzzi, 2006; NICE Guidelines, 2010; Cowie et al, 2010) and as a prognostic aid (Koglin et al., 2001). Interventions to reduce levels of BNP are clearly of importance in the management of CHF, and evidence demonstrates that pharmacotherapy can reduce BNP as a result of the favourable effects on cardiac remodelling (McCullogh, 2004). BNP levels have been used to guide up-titration of HF medication (Januzzi and Troughton, 2013) and the effects of exercise training on BNP and NT-proBNP levels have also been reported. With such a magnitude of standard deviation it is essential that a standardised blood sampling technique is used otherwise the evidence might be considered equivocal (Smart and Steele, 2010). In their meta-analysis (Table 1.6) Smart and Steele (2010) demonstrated that a course of exercise training did significantly lower BNP and NT-proBNP levels. Their systematic review of nine randomised, controlled studies included 250 exercise participants and 213 controls. Most were males aged 53 to 75 years and New York Heart Association (NYHA) class I to III; six studies measured NT-proBNP and two studies measured both BNP and NT-proBNP. Seven of the selected individual studies demonstrated that moderate intensity exercise training reduced BNP and NT-proBNP independent of frequency and duration of training, perhaps due to a

blunted neurohormonal response at rest, resulting in a reduction in BNP release (Passino et al., 2006). Two studies (Butterfield et al., 2008; Jónsdóttir et al., 2006) had low weekly energy expenditure of less than 400Kcal/week and changes in BNP and NT-proBNP were not significant, therefore the authors concluded from their analysis that a minimum weekly energy expenditure of 400 to 450 Kcal may be required to elicit similar positive results. In contrast to most UK CR programmes, where a circuit based approach to exercise training is implemented, eight of the studies used cycling as the only mode of exercise. Training frequency was between two and seven sessions weekly for three to nine months, with an intensity between 50% and 70% of maximum peak VO_2 and a session duration of 30 to 50 minutes. The authors carried out a sensitivity analysis: for NT-proBNP this involved the removal of the studies that showed large standard deviation - and confirmed that changes in both BNP and NT-proBNP remained statistically significant. When assessing study quality the authors found that six of the studies had standardised the timing of the blood sampling, but only two provided information regarding inter-assay coefficient of variation. Only two studies provided sufficient detail about randomisation, four studies provided information regarding recruitment and only three provided details of adherence to exercise training. In 2011 Smart et al. carried out an individual patient meta-analysis (Table 1.6) and confirmed previous findings, namely exercise training was able to modulate BNP and NT-proBNP levels in patients with CHF. Ten randomised, controlled studies met their inclusion criteria, with 313 exercise participants and 252 controls. Exercise and control group participants were matched at baseline in nine studies; 80% were male and were NYHA class I to III. As with the previous review, all but one study

used cycling as the mode of exercise training, the frequency was two to seven sessions per week, intensity 50 to 95% of peak VO_2 , 30 to 50 minutes per session and three to nine months duration. Mean weekly energy expenditure was 457 ± 135 Kcal per week. Again, two studies with the lowest energy expenditure did not show significant changes in BNP. Overall, compared to the control group, exercise training significantly lowered BNP (-28.3%, $p < 0.0001$) and NT-proBNP (-7.4%, $p < 0.0001$). After sensitivity analysis, removing two studies where energy expenditure could not be calculated, significant changes in BNP remained. To add further strength to the evidence base, the authors examined the relationship between changes in BNP/NT-proBNP and peak VO_2 . Baseline measures of peak VO_2 and BNP ($r = -0.33$, $p < 0.001$) and NT-proBNP ($r = -0.32$, $p < 0.001$) were both inversely correlated. Correlation coefficients also showed inverse relationships between change in peak VO_2 and change in BNP and NT-proBNP ($r = -0.31$, $p < 0.0001$; $r = -0.21$, $p = 0.001$ respectively) and change in BNP was also related to energy expenditure ($r = -0.19$, $p = 0.04$). Patients with a positive training response showed a greater reduction in both BNP and NT-proBNP ($p < 0.003$), and those with LVEF $< 34\%$ showed greater improvements in BNP ($p = 0.003$) and NT-proBNP ($p = 0.002$). Further data analysis suggested that the use of beta-blockade medication did not attenuate exercise training effects on BNP and NT-proBNP.

As mentioned above, factors other than CHF can affect BNP levels therefore it is important to take these into consideration. BNP levels are influenced by age and gender (elderly females have higher BNP levels than males), by obesity, liver cirrhosis and renal failure (Peacock, 2002). Pharmacotherapy also affects

BNP concentrations: ACE inhibitors and diuretics will reduce BNP levels (Cowie et al., 2003), but the effects of beta-blockade medication are equivocal with studies showing an increase, a decrease or no change (Olsson et al., 2007). Although third generation beta-blockers such as carvedilol lack the cardioselective (beta¹-selective) properties of second generation beta blockers such as bisoprolol and metoprolol, they do have additional vasodilating properties which could account for the varying results. Vasodilators and diuretics reduce plasma natriuretic peptide levels through reductions in intracardiac pressures (Davis et al., 2006); however, there is often an initial increase in circulating levels. Davis et al. (2006) demonstrated that the introduction of metoprolol increased plasma natriuretic peptides over several weeks/months without causing deterioration in CHF symptoms. There was a subsequent reduction that possibly reflected the attainment of reverse remodeling of the left ventricle.

Table 1.6 Summary of studies: effects of exercise training on BNP levels

Study	Participants	Protocol	Key Findings
Responders			
Conraads VM, Beckers P, Vaes J et al. (2003)	<p>Non-randomised study</p> <p>Intervention group: 27 patients with CHF</p> <p>Control group: 22 patients unable to attend exercise programme</p> <p>Stable condition on medical therapy for at least 1 month prior</p>	<p>Treadmill CPET. NT-proBNP level. Fasting blood samples taken between 8 and 9am.</p> <p>Intervention: 4-months combined endurance/resistance training programme. 3 x per week for 1 hour.</p>	<p>NT-proBNP levels reduced significantly after training (2124 ± 397 pg/ml before, 1635 ± 304 pg/ml after; $p = 0.015$).</p> <p>Limitations: small sample size, non-randomised study, possibility of selection bias.</p>
Giallauria F, De Lorenzo A, Pilerici F et al (2006)	<p>Randomised study</p> <p>Intervention group: 22</p> <p>Control group: 22</p>	<p>Cycle CPET. NT-proBNP levels. Fasting blood samples obtained between 8am and 9am.</p> <p>Intervention: 3-months endurance training programme. 3 x per week.</p>	<p>3 months training reduced NT-proBNP from 1498 ± 438 pg/ml at baseline to 470 ± 375 pg/ml ($p = 0.003$).</p> <p>Limitations: small sample size, predominantly male, mean age < 56 years, LVEF indicates only mild/borderline LVSD.</p>

Study	Participants	Protocol	Key Findings
Passino C, Severino S, Poletti R et al (2006)	<p>Randomised study</p> <p>Intervention group: 44</p> <p>Control group: 41</p> <p>Stable condition on optimal medical therapy</p>	<p>Cycle CPET. Echocardiography. Quality of life questionnaire. BNP and NT-proBNP levels.</p> <p>Intervention: 9-months endurance (cycling) training programme. Minimum 3 x per week.</p>	<p>Significant changes in baseline BNP (187 ± 29 ng/l) compared with post exercise BNP (123 ± 23 ng/l; $p < 0.01$) and NT-proBNP (baseline $1,370 \pm 234$ ng/l, post exercise 929 ± 206 ng/l; $p < 0.05$).</p> <p>Limitations: The study recruited predominantly males, under the age of 65 years.</p>
Sarullo FM, Gristina T, Brusca I et al. (2006)	<p>Randomised study</p> <p>Intervention group: 30</p> <p>Control group: 30</p> <p>Stable condition on medical therapy in the 3 months before the study</p>	<p>Cycle CPET. Echocardiography. NT-proBNP levels. Quality of life questionnaire.</p> <p>Intervention: 3 months endurance (cycling) training programme. 3 x per week for 30 minutes, 60 to 70% of VO_2 peak.</p>	<p>NT-proBNP levels decreased significantly in the exercise group compared with baseline (baseline 3376 ± 3133 pg/ml, post training 1434 ± 1673 pg/ml; $p = 0.0001$).</p> <p>Limitations: mean age for both the intervention group and the control group < 55 years therefore not necessarily representative of patients attending routine UK-based cardiac rehabilitation programmes.</p>

Study	Participants	Protocol	Key Findings
Passino C, Del Ry S, Severino S et al (2008)	Randomised study Intervention group: 71 Control group: 19 Stable systolic heart failure, optimal medical treatment	CPET. Echocardiography. BNP levels. Blood samples obtained at rest between 8am and 9am. Intervention: 9 month home based endurance (cycling) training programme. 3 x per week for 30 minutes, at 65% of VO_2 peak.	BNP decreased significantly in the exercise group from 179 ± 23 ng/l at baseline to 129 ± 19 ng/l ($p < 0.001$) post training. Limitations: low prevalence of females in the study population.
Rengo G, Pagano G, Parisi V et al. (2014)	Non randomised study No control group 221 patients completed an exercise programme Stable symptoms for 1 month, on optimal medical therapy apart from beta blockers. Existing co-morbidities	Cycle CPET. 6MWT. NT-proBNP. Fasting blood samples obtained at rest between 8am and 9am. Quality of life questionnaire. Intervention: 3 months structured exercise training. 2 - 3 x per week.	NT-proBNP reduced from 2111.4 ± 1145.6 pg/ml at baseline to 1532 ± 851.5 pg/ml post training ($p < 0.0001$). Limitations: non randomised, no control group. Low use of beta blockers reported.

Study	Participants	Protocol	Key Findings
<i>Non responders</i>			
Jónsdóttir S, Anderson KK, Sigurðsson AF, Sigurðsson SB (2006)	<p>Randomised study</p> <p>Intervention group: 21 patients</p> <p>Control group: 22 patients</p> <p>Previously hospitalised due to heart failure</p>	<p>Cycle CPET. 6MWT. Muscle strength test. ANP and BNP levels. Echocardiography. Quality of life questionnaire. Rehospitalisation.</p> <p>Intervention: 5-months combined endurance/resistance training programme. 2 x per week.</p>	<p>No significant difference in BNP levels post training.</p> <p>Limitations: small sample size, only included patients who were able to complete a symptom-limited exercise test therefore results may not be representative of all CHF patients.</p>
Butterfield JA, Faddy SC, Davidson P and Ridge B (2008)	<p>Randomised study</p> <p>Intervention group: 13</p> <p>Control group: 6</p> <p>Subgroup recruited from the St. George Living with Heart Failure study</p>	<p>6MWT. BNP levels. Blood samples obtained at rest between 2pm and 3pm. Quality of life questionnaire.</p>	<p>No significant difference in BNP levels post training.</p> <p>Limitations: small sample size of 14 males and 5 females.</p>

Study	Participants	Protocol	Key Findings
<p>Nilsson BB, Westheim A, Risberg MA et al. (2010)</p>	<p>Randomised study</p> <p>Intervention group: 39</p> <p>Control group: 39</p> <p>Stable condition for 4 weeks on optimal medical therapy.</p>	<p>Cycle CPET. 6MWT. NT-proBNP. Fasting blood samples obtained at rest between 8am and 9am. Quality of life questionnaire.</p> <p>Intervention: 4 months aerobic interval training programme, including 3 intervals of high intensity (15 – 18 on the Borg Scale). 2 x per week for 50 minutes.</p>	<p>No significant changes from baseline to post exercise.</p> <p>Limitations: relatively small sample size. The study included patients with signs of heart failure but preserved LVEF (> 40%).</p>

Study	Participants	Protocol	Key Findings
Meta-analyses and reviews			
Smart NA and Steele M (2010)	Evidenced based analysis of benefits of exercise on natriuretic peptide expression	<p>Systematic search for randomised controlled trials examining the effects of exercise training (aerobic and/or resistance) on BNP and/or NT-proBNP. 9 trials met the eligibility criteria.</p> <p>Individual patient data for 565 patients.</p>	<p>Exercise training with a weekly expenditure of more than 400 Kcal reduced BNP (mean difference -79 pg/ml, 95% CI -141 to -17 pg/ml, $p = 0.01$) and NT-proBNP (mean difference -621 pg/ml, 95% CI -844 to -398 pg/ml, $p < 0.00001$).</p> <p>Limitations: Patients recruited to the included studies were mostly male (50 – 91%); mean age range 53 to 75 years.</p>
Smart NA, Meyer T, Butterfield JA et al (2011)	Evidenced based analysis of benefits of exercise on natriuretic peptide expression	<p>Meta-analysis of the effect of exercise training on BNP expression in heart failure. 10 trials met the eligibility criteria.</p> <p>Individual patient data for 565 patients.</p>	<p>Exercise training reduced BNP (-28.3%, $p < 0.0001$) and NT-proBNP (-37.4%, $p < 0.0001$). Change in BNP ($r = -0.31$, $p < 0.0001$) and NT-proBNP ($r = -0.22$, $p < 0.0001$) were correlated with peak VO_2 change.</p> <p>Limitations: 80% of the patients recruited to the included studies were male, mean age of 60 years (62 years in control group).</p>

1.4.3 The link between BNP and remodelling of the left ventricle

Left ventricle remodelling is a process characterised by changes in wall thickness and enlargement of the left ventricle cavity (Giallauria et al., 2006). BNP and NT-proBNP levels correlate with left ventricular end-diastolic pressure and impaired LVEF (Rengo et al., 2014). Elevated end-diastolic pressure is linked closely with dyspnoea in patients with CHF (McCullough, 2004). It is therefore unsurprising that levels also correlate with heart failure severity and NYHA class (Sakurai et al., 2003) and with outcomes (Doust et al., 2005). Several studies investigating the effect of exercise training on BNP and NT-proBNP levels have found a reduction in post training natriuretic peptide levels and a corresponding increase in LVEF (Passino et al., 2006; Passino et al., 2008; Rengo et al., 2014), a reduction in end-diastolic volume (EDV) (Conraads et al., 2004; Passino et al., 2006) and an increase in E-wave and E/A ratio (Conraads et al., 2004; Giallauria et al., 2006). In contrast, Sarullo et al. (2006) found no change in LVEF or in the diameter of the left ventricle despite a post exercise training reduction in NT-proBNP levels. And although the NT-proBNP levels remained unchanged following HIIT in their study, Nilsson et al. (2010) found an inverse correlation between NT-proBNP and LVEF. Their study included CHF patients with preserved ejection fraction; data from these patients could have skewed the overall results and unfortunately the authors failed to complete a sub-group analysis.

From the results of published research studies and meta-analyses it appears that exercise training competes with the pathophysiologic afferent stimuli and mechanisms responsible for many of the signs and symptoms of the failing

heart, thereby complimenting pharmacotherapy (Gaderman et al., 2007) to reduce circulating plasma BNP levels. Study 4 (Chapter 5) examined the effect of moderate-intensity exercise training, following current UK guidelines, on circulating NT-proBNP levels in CHF patients who were optimised on beta-blockers and ACE inhibitors.

1.5 Effects of exercise training on remodelling of the left ventricle in patients with CHF

1.5.1 Introduction

Patients often remain symptomatic even when on optimum CHF medication (Giannuzzi et al., 2003). Left ventricle remodelling is significant in the progression of HF and involves several factors, including haemodynamic and neurohormonal derangement. Remodelling is characterised by changes in left ventricle dimensions and continues long after healing following acute myocardial infarction (AMI) (Giallauria et al., 2008). The term remodelling, initially seen following AMI, has since extended to cardiomyopathies of non-ischaemic origin (Pieske, 2004). There is progressive chamber enlargement and deterioration in “pump” function as a result of increased haemodynamic load and neurohormonal stress (Haykowsky et al., 2007). End-diastolic volume (EDV) and end-systolic volume (ESV) increase; there is wall thinning and a change in left ventricle shape, usually accompanied by a reduction in LVEF. This results in worsening systolic and diastolic function, development of mitral regurgitation and increased incidence of arrhythmias (Pieske, 2004).

1.5.2 Remodelling following exercise training in CHF patients

Meta-analysis data have shown that aerobic exercise training improves LVEF, EDV and ESV in patients with stable CHF due to systolic dysfunction (Haykowsky et al., 2007; Chen et al., 2012). The effects of combined aerobic and resistance training or isolated resistance training remain inconclusive. Although resistance training is not associated with improvements in left ventricular remodelling, it does not appear worsen it. The weighted mean difference (WMD) in LVEF from 9 trials, and the EDV and ESV from 5 trials in the meta-analysis by Haykowsky et al. (2007) was significantly different following aerobic training (Table 1.7). The use of beta-blockers in the included studies was low and the number of studies examining the effects of exercise training on EDV and ESV was small (7 in total). The subsequent meta-analysis by Chen et al. in 2012 (Table 1.7) included 8 new randomised controlled trials, with 15 trials in total (813 patients; 425 in the exercise group and 338 in the control group). As with many studies recruiting patients with CHF, the study populations included relatively young patients (mean age ranged from 54 to 75 years), who were predominantly male. Twelve of the included studies examined the effects of aerobic exercise training at an intensity between 60% and 80% of VO_2 peak. Only three studies examined the effects of combined aerobic and strength training and one examined strength alone, which may account for the inconclusive results when data were pooled in meta-analyses. The general outcome of this meta-analysis was in accordance with that of Haykowsky et al. (2007). Aerobic exercise training was associated with a significant increase in LVEF (standardised mean difference (SMD) = 0.44; 95% CI 0.28 to 0.61), with long-term (≥ 6 months) aerobic training achieving superior results to short-term

training. Overall, exercise training was not associated with an improvement in EDV and ESV; however aerobic training alone led to significant improvements in both EDV (SMD = -0.33; 95% CI -0.49 to -0.16) and ESV (SMD = -0.40; 95% CI -0.57 to -0.23). Again, long-term (≥ 6 months) aerobic training had a greater effect on EDV and ESV but there was no evidence of benefit with short-term training.

Included in the meta-analysis by Chen et al. (2012) were data from Wisløff et al.'s study (2007) which demonstrated that HIIT at 95% of maximal heart rate elicited greater improvements in systolic function. They recruited 27 elderly patients (75.5 ± 11.1 years) with CHF following AMI and randomised them into 3 groups: HIIT, moderate continuous training (MCT) and a control. 12-weeks of HIIT induced reverse remodelling, but there was no significant difference in the MCT or control groups. Following HIIT, left ventricle EDV and ESV reduced by 18% and 25% respectively ($p < 0.01$) and LVEF increased from $28 \pm 7\%$ to $38 \pm 10\%$ ($p < 0.01$). There was a corresponding 40% reduction in NT-proBNP levels ($p < 0.02$), which further reflects the effectiveness of HIIT in modifying remodelling. The authors suggest that HIIT has an effect on EDV and ESV similar to that of 3-months of cardiac resynchronisation therapy and an effect on LVEF similar to that of combined treatment with ACE inhibitors and beta-blockers. Diastolic function also improved significantly following HIIT demonstrated by an improved E/Ea ratio which suggests a reduction in filling pressure. Malfatto et al. (2009) also found evidence of improved diastolic function in their study, reporting improved left ventricular diastolic stiffness.

Giannuzzi et al. (2003) were first to investigate the anti-remodelling effects of long term (>6 months) exercise training in patients with stable CHF. They recruited 90 patients to their multicentre study, and randomised them into a 6-month exercise training programme or a control group. In the exercise group 91% of patients were prescribed ACE inhibitors, but only 22% were taking beta-blockers. The percentage taking beta-blockers was actually higher than in previous studies, and was equal between the 2 groups. Therefore the benefits seen following exercise training were in addition to those elicited by prescribed medication. After six months of moderate intensity exercise training EDV and ESV had reduced in the intervention group (EDV from 142 ± 26 ml/m² to 135 ± 26 ml/m², $p < 0.0006$; ESV from 107 ± 24 ml/m² to 97 ± 24 ml/m², $p < 0.05$) but had increased significantly in the control group. LVEF also increased by 16% ($25 \pm 4\%$ to $29 \pm 4\%$; $p < 0.001$) in the intervention group but was unchanged in the control group. The authors suggested that the significant decrease seen in resting blood pressure and sub-maximal rate pressure product in the exercise group may have favourably affected LV wall tension, which could have attenuated the abnormal remodelling process. In 2008, Giallauria et al. found similar results in 30 post infarction patients with moderate LVSD following a 6-month exercise training programme. Patients enrolled into this study were, again, relatively young – in the intervention group the mean age 56 ± 3 years, patients were predominantly male (73%) and had a mean LVEF $42 \pm 11\%$. Nonetheless exercise training resulted in a 9% ($p < 0.001$) reduction in left ventricle end-diastolic volume index (LVEDVI) and a 71% ($p < 0.001$) reduction in circulating NT-proBNP. E-wave and E/A ratio increased following training, suggesting an exercise-induced decrease in left ventricle wall stress. This is

confirmed by the observed correlation between the decrease in NT-proBNP and the change in left ventricle volumes and by the inverse correlation between changes in NT-proBNP and changes in E-wave. However, it appears that CHF medication was still being titrated to the maximal dose during the study, therefore the effects of medication on the observed improvements cannot be ruled out. Subsequent studies have since confirmed these results as referred to above in the meta-analysis by Chen et al. (2012) and as detailed in Table 1.7. Suggested mechanisms for the anti-remodelling effects of aerobic exercise training seen in published studies include reduced sympathetic tone and decreased resting circulating neurohormones, thereby counteracting the possible deleterious effects of neurohormonal activation seen in CHF. Improved sympathovagal balance combined with a decrease in vasoconstrictive neurohormones will lead to a reduction in vascular load which may attenuate left ventricle remodelling. Increased LVEF seen after a period of aerobic exercise training is most likely due to enhanced preload, myocardial contractility and vascular reserve (Haykowsky et al., 2007).

In summary, data demonstrate that long-term aerobic training (≥ 6 months) of moderate to high intensity reverses left ventricular remodelling in clinically stable patients with CHF; these beneficial effects are supplementary to pharmacotherapy. In Study 4 (Chapter 5) echocardiography studies were used to examine changes in left ventricular modelling in a sub-group of patients from the cohort.

Table 1.7 Summary of studies: effects of exercise training on remodelling

Study	Participants	Protocol	Key Findings
Responders			
Hambrecht R, Gielen S, Linke A et al. (2000)	Randomised study Intervention group: 36 Control group: 37 Clinically stable for 3 months	Intervention: 2 weeks – exercised in hospital 4 to 6 times daily. On discharge from hospital patients exercised daily for 20 minutes for 6 months.	Resting LVEF % increased from 30 ± 8 to 35 ± 8 ($p = 0.003$). Left ventricle EDD reduced by 3 ± 6 mm ($p < 0.001$). Left ventricle ESD reduced by 5 ± 7 mm ($p < 0.001$). EDV reduced by 22 ± 53 ml ($p = 0.008$) and ESV by 24 ± 36 ml ($p = 0.009$). Limitations: no females, the mean age of 55 years is relatively young and the use of beta-blockers was low.
Giannuzzi P, Temporelli PL, Corrà U and Tavazzi L for the ELVD-CHF Study Group (2003)	Randomised study Intervention group: 45 Control group: 45 Stable on optimal medication for 3 months	Intervention: 6 month supervised cycle training programme.	EDV and ESV had reduced in the intervention group (EDV from 142 ± 26 to 135 ± 26 , $p < 0.0006$; ESV from 107 ± 24 to 97 ± 24 , $p < 0.05$) but had increased significantly in the control group. LVEF % increased from 25 ± 4 to 29 ± 4 ($p < 0.001$). No change in the control group. Limitations: Young patients, predominantly men.
Passino C, Severino S, Poletti R et al. (2006)	Randomised study Intervention group: 44 Control group: 41 Stable condition on optimal medical therapy	Intervention: 9-months cycling. Minimum 3 x per week, 30 minutes cycling at 60 rpm.	Mean LVEF % increased to 38 ± 2 ($p < 0.01$) post training. No increase in the control group. EDV and ESV normalised for body surface area (EDVi and ESVi) reduced significantly (EDVi from 111 ± 8 ml/m ² to 96 ± 6 ml/m ² , EDVi from 72 ± 6 ml/m ² to 58 ± 5 ml/m ² ; $p < 0.05$). Limitations: The study recruited predominantly males, under the age of 65 years.

Study	Participants	Protocol	Key Findings
Conraads VMA, Vanderheyden M, Paelinck B et al. (2007)	Randomised study Intervention group (with CRT): 8 Control group (No CRT): 9 Clinically stable on optimum medication for 1 month	Intervention: ambulatory exercise programme 3 x per week for 1 hour (50 minutes cycling/walking) for 5 months.	Both groups benefitted equally in terms of LV remodelling – LVEDD and LVESD diameters were reduced and LVEF % was significantly increased. Limitations: small number of patients enrolled to each group was small.
Klecha A, Kawecka-Jaszcz K, Bacior B et al. (2007)	Randomised study Intervention group: 25 Control group: 25 Stable condition on optimal medical therapy for at least 6 weeks	Intervention: 3 x per week for 6 months; 25 minutes cycling at a maximum of 80% of the predicted heart rate at peak VO_2 .	There was no significant change in the LV although there was a trend towards an improvement in LVEF % (27.4 ± 5.7 to 30.2 ± 7.8) and EDV (ml/m^2) (122.6 ± 20.1 to 114.8 ± 19.3). Limitations: due to the restricted inclusion and exclusion criteria the population recruited in this trial may not be representative of a typical clinical population attending cardiac rehabilitation.
Wisløff U, Støylen A, Loennachen JP et al. (2007)	Randomised study HIIT intervention: 9 MCT intervention: 9 Control: 9 All patients stable on optimal medication	HIIT: 90 – 95% peak HR MCT: 70 – 75% peak HR	Following HIIT left ventricle EDV and ESV reduced by 18% and 25% respectively ($p < 0.01$), LVEF % increased from 28.0 ± 7.3 to 38.0 ± 9.8 ($p < 0.01$) and Ea improved by 49% ($p < 0.01$) and the E/A ratio by 15% ($p = 0.05$). Both HIIT and MCT reduced E/Ea by 26% ($p = 0.001$) and 15% ($p = 0.043$). Limitations: small number of patients in each group.

Study	Participants	Protocol	Key Findings
Giallauria F, Cirillo P, Lucci R et al. (2008)	Randomised study Intervention group: 30 Control group: 31	Intervention: 6 month supervised cycle training programme. 3 x per week for 30 minutes, at 60 - 70% of VO ₂ peak.	Following training E-wave increased (pre training 59.5 ± 6.3 , post training 65.2 ± 6.6 ; $p < 0.001$), E/A ratio also increased (pre training 0.98 ± 0.1 , post training 1.22 ± 0.2 ; $p < 0.001$). LVEDVI decreased following training (pre training 107.3 ± 18.8 , post training 97.4 ± 17.9 ; $p < 0.001$). Limitations: the study involved relatively young patients, predominantly men. It appears that CHF medication was still being titrated to the maximal dose during the study.
Malfatto G, Branzi G, Osculati G et al. (2009)	Randomised study Intervention group: 27 Control group: 427 No change in pharmacological treatment allowed	Intervention: cycle or treadmill x 40 minutes, 3 x per week for 3 months.	No significant change in LVEF % or EDV following exercise training. E/A reduced from 1.59 ± 0.08 to 1.11 ± 0.59 ($p < 0.02$).
Palevo G, Keteyian SJ, Kang M and Caputo JL. (2009)	Randomised study Intervention group: 10 Control group: 6	Intervention: 8-weeks of strength training, 3 sessions per week.	There was a significant improvement in LVEF % (32 ± 12 pre training to 37 ± 10 post training, $p < 0.05$). There was a slight (NS) increase in EDV, and a slight (NS) reduction in ESV. Limitations: small sample size of 16 subjects (1 female).

Non-responders			
Belardinelli R, Georgiou D, Cianci G and Purcaro A (1999)	<p>Randomised study</p> <p>Intervention group: 50 Control group: 49</p> <p>All patients stable for at least 3 months</p>	<p>Intervention: 3 x per week cycling for 8 weeks at 60% of VO_2 peak followed by a 12 month maintenance programme</p>	<p>No significant change in LVEF, EDV or ESV.</p> <p>Limitations: mainly males with ischaemic aetiology.</p>
McKelvie RS, Teo KK, Roberts R et al. (2002)	<p>Randomised study</p> <p>Intervention group: 90 Control group: 91</p>	<p>Intervention: 3-month supervised exercise training programme 2 x per week. Followed by 9 months of home-based exercise training</p>	<p>No significant changes seen in LVEF, EDV and ESV.</p>
Myers J, Wagner D, Schertler T et al. (2002)	<p>Randomised study</p> <p>Intervention group: 12 Control group: 12</p>	<p>Intervention: 5 x 45 minute supervised cycling per week for 2 months, at 60 – 80% of VO_2 max</p>	<p>There was no significant change in LVEF, EDV or ESV.</p> <p>Increased relaxation velocity suggests an improvement in diastolic function.</p> <p>Limitations: short training period of 2 months and small number of patients in each group.</p>

Study	Participants	Protocol	Key Findings
Klocek M, Kubinyi A, Bacier B and Kawecka-Jaszcz K (2005)	Randomised study Intervention group A: 14 Intervention group B: 14 Control group: 14 Stable condition on optimal medical therapy for at least 3 months	Intervention A: 4 minute cycle at 60% of maximal heart rate followed by 1 minute rest, repeated 5 times, 3 x per week for 6 months. Intervention B: as above with 4 minute cycle at an increasing load	There was no improvement in LVEF %, LVDD, LVSD, E-wave or E/A ratio following training. Limitations: the study was relatively small consisting exclusively of men of a young age.
Jónsdóttir S, Anderson KK, Sigurðsson AF, Sigurðsson SB (2006)	Randomised study Intervention group: 21 Control group: 22	Intervention: 5-months combined endurance /resistance training 2 x per week	No significant improvement found in LVEF %. Limitations: small sample size, only included patients who were able to complete a symptom-limited exercise test therefore results may not be representative of all CHF patients.
Fraga R, Franco FG, Roveda F (2007)	Randomised study Intervention group: 15 Control group: 12	Intervention: 4 months aerobic and strength exercises, 3 x 60 minute sessions per week	No significant change in LVEF % or end diastolic diameter. Limitations: small study population of young patients with CHF and only a small number due to IHD.

Study	Participants	Protocol	Key Findings
Mandic S, Tymchak W, Kim D et al. (2009)	Randomised study Intervention: aerobic exercise n = 14 Intervention: aerobic and resistance exercise n = 15 Control group: 13	Intervention: 30 minutes, 3 x per week for 12 weeks of either aerobic training at 50 – 70% of HRR or combined aerobic and resistance training	Neither aerobic training nor combined aerobic and resistance training improved resting left ventricular cavity size or systolic function. Limitations: small sample size. One third of patients experienced a change in medication during the 12-week intervention period.
Santos JMT, Kowatsch I, Tsutsui JM et al. (2010)	Randomised study Intervention group: 13 Control group: 10 Optimised medication	Intervention: 4-month cycling programme, 3 x 25 minute per week plus 10 minutes strength exercise	No changes in LV remodelling or systolic function following training. Limitations: small sample size in each group. Mean values not reported.
Meta-analyses and reviews			
Haykowsky MJ, Liang Y, Pechter D et al. (2007)	Evidenced based analysis of benefits of exercise on left ventricle remodelling	Meta-analysis of the effect of exercise training on left ventricular remodelling in heart failure patients. 14 trials reported LVEF data (n = 812 patients). 7 trials reported both EDV and ESV data (n = 569 patients).	9 trials of aerobic training reported an increase in LVEF (9 trials, 538 patients; WMD = 2.59%; 95% CI 1.44% to 3.74%. $I^2 = 17.2\%$). 5 trials of aerobic training reported a decrease in EDV (371 patients; WMD = -11.49ml; 95% CI -19.95 to -3.02ml) and ESV (371 patients; WMD = -12.87ml; 95% CI -17.80 to -7.93ml). Limitations: the majority of patients were clinically stable younger men. There was a low use of beta-blockers.

Study	Participants	Protocol	Key Findings
Smart N (2011)	Evidenced based analysis of benefits of exercise	Meta-analyses and randomised, controlled trials reviewed from a search of PubMed, Cochrane Controlled Trial Registry, CINAHL and EMBASE in order to make recommendations.	Recommendations: “Evidence suggests exercise training will improve systolic function and should be predominantly aerobic, and if tolerated, intermittent high intensity in nature as this will convey the greatest improvements in systolic function.” “Evidence suggests exercise training may enhance diastolic function.”
Chen YM, Li ZB, Zhu M and Cao YM. (2012)	Evidenced based analysis of the benefits of exercise, based on the meta-analysis of Haykowsky et al. to provide an update. There was a high use of beta- blockers in 8 recent trials.	Meta-analysis of the effect of exercise training on left ventricular remodelling in heart failure patients. 8 additional RCTs met the inclusion criteria.	12 trials of aerobic training reported an increase in LVEF (SMD = 0.44; 95% CI 0.28 to 0.61). 12 trials of aerobic training reported a significant decrease in EDV (574 patients; SMD = -0.33; 95% CI -0.49 to -0.16) and ESV (11 trials; 548 patients; SMD = -0.40; 95% CI -0.57 to -0.23). Long term aerobic exercise (≥ 6 months) had marked positive effect on EDV and ESV. Effects of combined or strength training alone were inconclusive. Limitations: the majority of participants were low-to-moderate risk males.

1.6 Effects of pulse pressure on exercise training outcomes in patients with CHF

1.6.1 Introduction

Pulse pressures (PP) can be calculated from the difference of the measured systolic and diastolic blood pressures (Blacher and Safar, 2005) using the following formula:

$$PP = P_{\text{systolic}} - P_{\text{diastolic}}$$

A low PP ≤ 20 mmHg caused by a low systolic blood pressure (SBP) (e.g. 90 mmHg) and a normal diastolic blood pressure (DBP) (e.g. 70 to 90 mmHg), may indicate a decreased cardiac output (Gopal et al., 2009) and reflects a reduction of stroke volume due to left ventricular dysfunction (Franklin et al., 1999). Wilson et al. (1996) concluded that patients with CHF and exercise intolerance fall into two general groups: i) those who have normal or nearly normal cardiac output during exercise and respond well to an exercise training programme (e.g. $>10\%$ increase in peak $\dot{V}O_2$), suggesting that skeletal muscle deconditioning is the major contributor to their exercise intolerance, and ii) those who exhibit a reduced cardiac output response to exercise. This latter group of patients do less well with CR, often finding exercise training exhausting. Thirty four percent of patients in their study had reduced cardiac output responses to exercise. The authors suggested that their exercise intolerance was due primarily to circulatory dysfunction (particularly low skeletal muscle flow) and suggested that

haemodynamic responses to exercise can define responders to exercise training.

1.6.2 The link between pulse pressure and cardiac index

A study by Stevenson and Perloff (1989) demonstrated a positive correlation between low PP and a reduced cardiac index (cardiac index = cardiac output indexed to body surface area) of $< 2.2 \text{ L/min/m}^2$ (Table 1.8). They confirmed that cardiac output can be assessed by PP and that it can be used to identify the presence of a severely reduced cardiac index rather than to estimate the exact cardiac index value. They analysed PP as a proportion of systolic pressure in their participants with known chronic dilated left ventricular failure ($n = 50$). It was found that a proportional PP of $< 25 \text{ mmHg}$ identified 91% of patients with a cardiac index $\leq 2.2 \text{ L/min/m}^2$ (normal cardiac index $2.5 - 4 \text{ L/min/m}^2$). Shelton et al. (2010) have more recently reported that, although cardiac index is significantly lower in patients with heart failure compared with controls at rest and during incremental exercise, there is no difference in the absolute increase in cardiac index from rest to a workload of 60 watts during cycle ergometer testing. This indicates that patients with a low PP/reduced cardiac index are able to increase their cardiac output in response to submaximal exercise. Furthermore, it may explain why these patients might actually still benefit from a course of exercise training.

1.6.3 The link between low pulse pressure and mortality

Low PP has been reported to be an independent predictor of mortality (Table 1.9) in patients with decompensated heart failure (Aronson and Burger, 2004),

in patients with advanced CHF (Voors et al., 2005; Petrie et al., 2009; Yildiran et al., 2010) and in patients with symptomatic left ventricular dysfunction post myocardial infarction (Petrie et al., 2007). Blood pressure data from 489 patients enrolled in the *Vasodilation in the Management of Acute Congestive (VMAC) HF study* were used by Aronson and Burger (2004) to determine the relationship between PP and survival in patients requiring hospitalisation for decompensated HF. At 6-months after hospital discharge low PP at baseline was a strong predictor of mortality with a 19% increment for each 10 mmHg decrease ($p = .0002$). In a separate analysis limited to patients in whom blood pressure readings were obtained within 24 hours of admission to rule out effects of medical therapy, there was an adjusted relative risk of mortality at 6 months of 4.2 (CI 95%, 2.0 to 8.6; $p < .0001$) in the lower PP tertile compared with the upper tertile. Furthermore, there was an adjusted 25% increment in mortality for each 10 mmHg decrease in baseline PP ($p = .001$). Voors et al. (2005) studied the link between PP and mortality in patients with advanced CHF, and also analysed the relationship between PP and natriuretic peptides. They reported that patients with a $PP \leq 35$ mmHg had a significantly lower survival and those with a PP below the median value of 45 mmHg had increased atrial natriuretic peptide (ANP) and B-type natriuretic peptide (BNP) levels. Petrie et al. (2007) studied the prognostic value of PP in patients 3 to 21 days post myocardial infarction, with a mean left ventricular ejection fraction (LVEF) of 33%. Using data from 1959 patients recruited to the CAPRICORN clinical trial they found that, in asymptomatic patients ($n = 1342$) PP was not predictive for any outcome. However in symptomatic patients ($n = 613$) low PP predicted all-cause mortality (HR 0.83 per 10 mmHg; CI 0.71 – .98; $p = .0252$), cardiovascular

mortality (HR 0.83; CI 0.70 – .98; $p = .0245$) and sudden death (HR 0.77; CI 0.60 – 1.00; $p = .0470$). Somewhat in contrast to these findings, PP was found to be an independent predictor of mortality and morbidity only in non-ischaemic HF patients in a study by Petrie et al. in 2009. This study cohort of 1901 patients enrolled in the PRIME II study, however, had a lower mean LVEF of 26% and advanced HF. In ischaemic HF ($n = 1118$) PP was not an independent predictor of all-cause mortality, but in non-ischaemic HF ($n = 783$) low PP was an independent predictor of all-cause mortality (HR 0.84 per 10 mmHg; $p = .036$). Furthermore, lower PP and higher NYHA class were the only independent predictors for first HF hospitalisation in both ischaemic and non-ischaemic patients. Yildiran et al. (2010) reported that previous studies of the prognostic value of PP in heart failure were performed only in specific patient groups - those with only mild or only advanced heart failure. Therefore, the prognostic value of PP is less clear when all NYHA classes are considered. The authors prospectively investigated a relationship between PP and 2-year cardiovascular death in 225 patients with CHF and a LVEF $< 40\%$, from all NYHA classes. Patients were monitored for a mean period of 670 ± 42 days for the occurrence of cardiovascular death. They observed low PP only in patients with advanced heart failure; PP decreased as NYHA class worsened ($p < .001$). Twelve patients were lost to follow-up during the study period and in the remaining 213 patients, 56 cardiac-related deaths (26.3%) occurred: 42 in patients with a PP of less than 35 mmHg, 9 in those with a PP of 35 to 45 mmHg, 3 in those with a PP of 46 to 55 mmHg, and 2 in those with a PP greater than 55 mmHg. Univariate analysis showed that PP was a predictor of death in the entire study cohort ($p < .01$) and multivariate logistic regression analysis

also revealed PP as an independent predictor of death across the cohort. Every 1 mmHg decrease in PP increased the risk of death by 24.2%. Furthermore, PP independently predicted death in the 178 patients with ischemic heart failure, in contrast to the findings by Petrie et al. (2009). In the patients with advanced heart failure, 48 cardiac-related deaths occurred, and the only independent predictor of death in this group was PP (OR=0.85; 95% CI, 0.79–0.916; $p < .001$).

To date there is only one published study relating to the effects of low PP on CHF patients attending CR (Leslie and Buckley, 2012). This retrospective study explored the effects of PP on CR outcomes in 86 patients with CHF and showed that PP did not influence the efficacy of exercise training. However, as a clear indicator of reduced cardiac index and predictor of mortality, it remains possible that PP might influence safety and outcomes in CR. This warrants further, more robust investigation under research conditions.

Table 1.8 Low pulse pressure: predictor of reduced cardiac index in CHF

Study	Participants	Diagnosis	Protocol	Key Findings
Stevenson LW and Perloff JK. (1989)	50 patients	CHF Non-ischaemic aetiology in 36 patients	Proportional PP defined as: $(\text{SBP} - \text{DBP})/\text{SBP}$	Proportional PP correlated well with cardiac index ($r = 0.82$; $p < 0.001$). A proportional PP $\leq 25\%$ identified 91% of patients with a cardiac index < 2.2 L/min/m ² . Conclusion: the adequacy of resting cardiac output is assessed reliably by proportional PP.

Table 1.9 Low pulse pressure: predictor of mortality in CHF

Study	Participants	Diagnosis	Protocol	Key Findings
Aronson D, Burger AJ (2004)	489 patients enrolled in the VMAC HF study	Decompensated HF requiring hospitalisation	Blood pressure measurements performed at baseline. PP divided into tertiles for comparison: first tertile $PP \leq 43$ mmHg; second 44 -58 mmHg; third ≥ 59 mmHg. 6-month follow up after hospital discharge.	Lower PP was predictive of an increase in all-cause mortality with a 19% increment for each 10 mmHg decrease ($p = 0.0002$). Conclusion: low PP is an independent predictor of mortality.
Voors AA, Petrie CJ, Petrie MC, Charlesworth A et al. (2005)	Data collected from 1901 patients enrolled in the PRIME II study	CHF	Blood pressure data from the PRIME II study were used to calculate PP.	<p>Patients with a PP <45 mmHg had lower SBP and DBP, lower LVEF and higher heart rate.</p> <p>Patients with a PP <35 mmHg had significantly lower survival ($p = 0.0005$).</p> <p>Patients with a PP <45 mmHg had significantly higher BNP ($p = 0.002$) and NT-proBNP ($p = 0.002$).</p>

Study	Participants	Diagnosis	Protocol	Key Findings
Petrie CJ, Robertson M, Voors AA et al. (2007)	Data from 1959 patients recruited to the CAPRICORN clinical trial	CHF	PP adjusted for other baseline risk factors including MAP and study treatment.	Low PP predicted all-cause mortality (HR 0.83 per 10 mmHg; p = 0.0252), cardiovascular mortality (HR 0.83; p = 0.0245) and sudden death (HR 0.77; p = 0.0470).
Petrie CJ, Voors AA, van Veldhuisen DJ. (2009)	Data collected from 1901 patients enrolled in the PRIME II study	Ischaemic HF n = 1118 Non-ischaemic HF n = 783	The study compares prognostic value of PP between patients with ischaemic and non-ischaemic advanced CHF.	In ischaemic HF PP was not a predictor of mortality. In non-ischaemic HF low PP was an independent predictor of mortality (HR 0.84 per 10 mmHg; p = 0.036)..
Yildiran T, Koc M, Bozkurt et al. (2010)	225 patients Median PP 40 mmHg.	CHF	Patients were monitored for a mean period of 670 ± 42 days for the occurrence of cardiovascular death. 12 patients lost to follow-up.	42/56 deaths in patients with a PP < 35 mmHg. Each 1 mmHg reduction in PP increased risk of death by 24.2%. PP was the only independent predictor of death in advanced HF.

1.7 Effects of exercise training on quality of life in patients with CHF

1.7.1 Introduction

Patients with CHF suffer from dyspnoea and fatigue, affecting their ability to perform activities of daily living which in turn leads to reports of deteriorating QoL (Holst et al., 2001; Giannuzzi et al., 2001). Moreover, depression is recognised as an independent risk factor for mortality and morbidity in patients with CHF regardless of the cause (Jiang et al., 2004). Depression is not uncommon in patients with chronic illness and 22% to 43% of patients with CHF suffer clinical depression (Powell et al., 2005; Rutledge et al., 2006). Exercise training is considered an effective treatment to improve QoL; as exercise capacity increases, patients with CHF experience less fatigue and dyspnoea and become more able to perform activities of daily living. This increased independence is associated with less depression and improved QoL (Giannuzzi et al., 2001). The BACPR (2012) and ACPICR (2009) standards recommend the use of valid and reliable measures of QoL for patients with CHF, such as the Hospital Anxiety and Depression Scale (HADS) (Zigmond and Snaith, 1983) and the disease specific Minnesota Living with Heart Failure (MLHFQ) questionnaire (Rector et al, 1987). The MLHFQ measures patient's perceptions of the effects of Heart Failure and its treatment on his or her daily life. The questionnaire uses a 21-item, self-administered questionnaire covering physical, socio-economic and psychological/emotional impairments associated with their heart failure. It allows a quantitative measure of the patient's perception of the extent of their impairment and how it is affected by therapeutic intervention and lower scores indicate an improvement in QoL (Smart and

Murison, 2012). The HADS is a tool to measure anxiety and depression. It is a self-assessment mood scale specifically designed for use in non-psychiatric hospital outpatient departments, and comprises of 14 items with weighted responses (0 to 3 points for each item). These items are divided into anxiety and depression subscales, and a score of 11 points or greater in either subscale indicates significant anxiety or depression (Zigmond and Smaith, 1983).

1.7.2 Quality of life following exercise training in CHF patients

In their systematic review of randomised controlled studies (Table 1.10), Lloyd-Williams et al. (2002) reported that QoL assessment scores were improved following a course of exercise training. The authors reviewed a total of 31 trials, only 14 (45%) of which were randomised controlled trials. Just over half (16) of the 31 studies reviewed included QoL as an outcome; 69% reported positive effects. However, they questioned the suitability of several of the QoL tools that were selected as they were not considered appropriate for patients with a chronic condition. Only 3 studies used the MLHFQ and none were reported to have used the HADS. There were several limitations to this review in addition to the large number of non-randomised controlled trials. In 67% of the 31 included trials the sample size was 25 participants or fewer, with only 13% of trials having a sample size of 51 to 150 participants. The authors did not pool data from the trials, perhaps due to the number of different scales used to assess QoL, therefore they were not able to provide an estimate of effect size. As with many of the studies recruiting CHF patients the mean ages were predominantly younger (in 74% of the trials the mean age was 65 years or less) and male and

patients with co-morbidities were often excluded. Rees et al. (2004) were also unable to undertake a pooled analysis in their systematic review due to the number of different scales used (Table 1.10). Only nine of 29 (31%) trials reported QoL as an outcome, five of which used the MLHFQ. There were no studies reported to have used the HADS. Significant improvements were seen in the short-term in four of five studies; one of two studies that measured QoL over the longer-term of 12 months found that the improvement was maintained. Again, the majority of the included trials were small, recruiting mostly men, and patients with co-morbidities were often excluded.

Table 1.10 Summary of meta-analyses and reviews: effects of exercise training on quality of life

Study	Participants	Protocol	Key Findings
Lloyd-Williams F, Mair FS and Leitner M. (2002)	Evidenced based analysis of benefits of exercise training in CHF patients.	Systematic review of the effect of exercise training on QoL in heart failure patients. 31 trials included. Sample sizes ranged from 25 or less to 150. Predominantly male. Patients with co-morbidities often excluded.	Positive effects on QoL reported in 69% of studies. Limitations: quantitative analysis not applied. Poor quality/inappropriate assessment/screening tools used in some studies. None of the studies used the HAD scale. 3 (19%) used the MLHFQ and 1 (6%) used a physical activity questionnaire.
Rees K, Taylor RS, Sigh S et al. (2004)	Evidenced based analysis of benefits of exercise training in CHF patients.	Systematic review of the effect of exercise training on CHF patients. 9/29 studies reported QoL as an outcome. 5/9 studies used the MLHFQ. 2/5 studies looked at long-term benefits	7/9 studies found an improvement in QoL. Significant improvements were seen in 4/5 over the short-term. 1 study showed improvement was maintained at 12 months. Limitations: small trials, recruiting mostly men. Patients with co-morbidities often excluded. Results, therefore, may not be generalisable to all patients with CHF. A variety of different questionnaires used.

Study	Participants	Protocol	Key Findings
van Tol BAF, Huijsmans RJ, Kroon DW et al. (2006)	Evidenced based analysis of benefits of exercise training on QoL in CHF patients.	Meta-analysis of the effect of exercise training on QoL in heart failure patients. 35 randomised controlled trials included. A total of 1486 patients included. 9 studies used MLHFQ.	MLHFQ scores decreased significantly when pooled (463 patients) by 9.7 points ($p = 0.0001$). Limitations: mean age and severity of CHF in the meta-analysis not representative of the CHF populations in epidemiological findings.
Rutledge T, Reis VA, Linke SE et al. (2006)	Meta-analysis of published associations between depression and HF.	Meta-analysis of 27 studies to show prevalence of depression in HF patients, magnitude of the relationship between depression and clinical outcomes and evidence for treatment efficacy.	Prevalence of depression in HF patients approximately 22%; higher in females. Two-fold risk of mortality in HF patients with a depressive disorder or depressive symptoms. In the trial using the HADS (Radzewitz et al., 2002) there were no significant changes in the answers relating to anxiety and depression between baseline and follow-up.
Davies EJ, Moxham T, Rees K et al. (2010)	Evidenced based analysis of benefits of exercise training in CHF patients.	Systematic review of the effect of exercise training on CHF patients. 10/19 trials reported valid QoL measure. 6/10 used the MLHFQ.	Significant improvements seen in QoL scores following exercise training. Limitations: significant heterogeneity in observations on QoL. On the MLHFQ, the exercise group was on average 10 points higher than controls. The generalisability of the findings may be limited.

Study	Participants	Protocol	Key Findings
Smart N (2011)	Evidenced based analysis of benefits of exercise in CHF.	Meta-analyses and randomised, controlled trials reviewed in order to make recommendations for exercise training for CHF patients.	<p>Summarised Lloyd-Williams et al.'s (2002) systematic review which demonstrated that QoL improved in 11 of 16 trials; furthermore the meta-analysis by van Tol et al. (2006) showed that patients with CHF can expect an improvement of almost 10 points in MLHFQ scores following exercise training.</p> <p>Recommendation:</p> <p>“Evidence is unequivocal for improvements in QoL.”</p>
Taylor RS, Sagar VA, Davies EJ et al. (2014)	Evidenced based analysis of benefits of exercise training in CHF patients.	<p>Systematic review of the effect of exercise training on CHF patients.</p> <p>19/33 trials reported valid QoL measure.</p> <p>13/19 trials used MLHFQ, 1/19 used HADS.</p>	<p>Pooled total MLHFQ scores at 12 months showed a clinically significant improvement with exercise training.</p> <p>3 trials that reported MLHFQ scores at follow-up longer than 12 months also showed a greater improvement in the intervention group compared with controls.</p> <p>Limitations: significant heterogeneity in the exercise-control difference in MLHFQ scores at follow-up.</p>

Table 1.11 Summary of studies included in the 2014 Cochrane Review which report Minnesota Living with Heart Failure Questionnaire scores or Hospital Anxiety and Depression scores following exercise training

Study	Participants	Intervention	Key Findings
Belardinelli R, Georgiou D, Cianci G and Purcaro A (1999)	99 patients randomised	Aerobic exercise 3 x per week for 8 weeks plus 12 month maintenance programme.	Mean exercise-control difference at follow-up -11.0 (95% CI -19.33 to -2.67).
Gottlieb SS, Fisher ML, Freudenberger R et al. (1999)	33 patients randomised	Aerobic exercise 3 x per week for 3 months at Borg 12 to 13.	No significant improvement in MLHFQ score at follow-up.
McKelvie RS, Teo KK, Roberts R et al. (2002)	181 patients randomised	Aerobic and resistance exercise 2 x per week, months, at 60 – 70% max HR.	No significant improvement in MLHFQ score at follow-up (-3.9 ± 1.9 , $p = 0.28$).
Koukouvou G, Kouidi E, Iacovides A et al. (2004)	26 patients randomised	Aerobic and resistance exercise 3 – 4 x per week for 6 months, at 50 – 75% peak VO_2 .	Significant improvement in QoL in trained patients.
Austin J, Williams R, Ross L et al. (2005)	200 patients randomised	Aerobic endurance training and low resistance training 2 x per week for 8 weeks.	Baseline score 41, 8 weeks post exercise 25.8 ($p < 0.001$), 24 weeks post exercise 22.9 ($p < 0.01$).
Passino C, Severino S, Poletti R et al. (2006)	85 patients randomised	Aerobic exercise > 3 x per week for 9 months at 65% max VO_2 .	MLHFQ score improved from 54 ± 5 pre exercise training to 32 ± 4 post training ($p < 0.01$).

Study	Participants	Intervention	Key Findings
Dracup K, Evangelista LS, Hamilton MA et al. (2007)	173 patients randomised	Aerobic and resistance exercise 4 x per week at 40 – 60% max HR.	There was no significant difference between the intervention and control groups in QoL.
Nilsson BB, Westheim A and Risberg MA. (2008)	80 patients randomised	Aerobic exercise 2 x per week for 4 months at Borg 15 – 18.	MLHFQ score reduced from 33 ± 18 at baseline to 22 ± 12 post exercise (p = 0.034) and 22 ± 14 at 12-month follow-up (p = 0.002).
Zwisler AD, Schou L, Soja AM et al. (2008)	91 patients randomised	Aerobic and resistance exercise 3 x per week for 6 weeks at 50% max HR.	Anxiety and depression did not improve significantly following exercise.
Jolly K, Taylor RS, Lip GY et al. (2009)	169 patients randomised	Aerobic and resistance exercise 5 x per week for 6 months at 70% of peak VO ₂ or Borg 12 – 13.	At 6 months, there was no between-group difference in the primary outcome MLHFQ score.
Davidson PM, Cockburn J, Newton PJ et al. (2010)	105 patients randomised	Aerobic exercise 1 x per week for 12 weeks. Intensity not reported.	QoL scores improved at 3 months compared with baseline (intervention group -4.37, P<0.0001; control group -3.52, P<0.01).
Gary RA, Dunbar SB, Higgins MK et al. (2010)	Comprehensive: 28 patients randomised	Aerobic exercise 3 x per week for 12 weeks at RPE < 15 plus CBT.	Mean exercise-control difference at follow-up -10.10.
	Exercise alone: 37 patients randomised	Aerobic exercise 3 x per week for 12 weeks at Borg < 15.	Mean exercise-control difference at follow-up -3.30.

Study	Participants	Protocol	Key Findings
Yeh GY, McCarthy EP, Wayne PM et al. (2011)	100 patients randomised	Intervention: aerobic exercise 2 x per week for 12 weeks. Intensity not reported.	Patients in the intervention (tai chi) group had greater improvements in MLHFQ scores, -19 (-23, -3) vs. 1 (-16, 3), $p = 0.02$).
Belardinelli R, Georgiou D, Cianci G and Purcaro A. (2012)	123 patients randomised	Intervention: aerobic exercise 2 – 3 x per week for 8 weeks supervised then 2 x per week maintenance at 60 – 70% max VO_2 for 10 years.	QoL score was significantly better in the intervention group (43 ± 12 vs. 58 ± 14 in the control group, $p < 0.05$).
Witham MD, Fulton RL, Greig CA et al. (2012)	107 patients randomised	Intervention: aerobic and resistance exercise 2 x per week for 24 weeks. Intensity not reported.	No significant changes in MLHFQ and HADS.

The reliability and validity of the MLHFQ is recognised, but in spite of this a more recent review by van Tol et al. (2006) showed that only 29% (9/31) of studies included in their meta-analysis used this questionnaire (Table 1.10). However, pooled data from these nine studies did show a significant decrease of almost 10 points, which is considered clinically meaningful (Piña et al., 2003). In fact a difference of four points or larger on the MLHFQ has been shown to represent a clinically important, meaningful difference for patients (McAlister et al., 2004). Interestingly, van Tol et al. (2006) reported that only one study could demonstrate a significant correlation between improvements in cardiorespiratory outcomes and QoL scores, suggesting that factors other than physical fitness determine a patient's perception of QoL. As with previous reviews, there were no trials reported to have used the HADS. However, a meta-analysis by Rutledge et al. (2006) did include one study that used the HADS to measure depression in an intervention study in patients with CHF (Table 1.10), which showed no significant improvement (49 ± 7 vs 48 ± 8 , $p = 0.39$).

It is worth noting that the HF-ACTION study examined the effects of exercise training on QoL (Flynn et al., 2009), but used the Kansas City Cardiomyopathy Questionnaire (KCCQ) as their chosen outcome measure. There were a considerable 1159 patients in the exercise training group (1171 in the control group) and the KCCQ score improved by a significant 5.2 points following exercise training. There was also an improvement of 3.3 points in the control group; however the 1.9-point difference was significant ($p < 0.001$). Neither group experienced significant changes beyond three months. The HF-ACTION

study was included in the 2010 Cochrane Review (Davies et al.). Nineteen trials (a total of 3647 patients; 2331 from the HF-ACTION study) met the inclusion criteria, only eight of which had been included in the previous Cochrane Review by Rees et al. (2004). Just over half (53%; 10/19) of the studies reported a validated measure of QoL with the majority using the MLHFQ (6/10). Pooled MLHFQ results were significant (random-effects mean difference -10.3, 95% CI -15.9 to -4.8; $p = 0.0003$) as were the results when all data were pooled. The significant result remained even when excluding HF-ACTION data (Table 1.10). The authors noted that there was significant heterogeneity in their observations on MLHFQ, with the exercise group on average 10 points higher than controls.

The above reviews and meta-analyses showed that exercise training programmes may provide some important improvements in QoL in patients with CHF. However, with the relatively young mean age of patients recruited to the studies and the frequent absence of co-morbidities is it not clear whether the results of these studies are transferrable to the general CHF population attending routine CR programmes in the UK. The recently published update of the Cochrane Review (Taylor et al., 2014) included 33 trials, 19 of which reported the use of a validated QoL measure; 13 used the MLHFQ and 2 used the HADS (Table 1.10 and Table 1.11). Again the majority of the included trials were small (26 trials had less than 100 participants; HF-ACTION, 2009 contributed 2331 participants) with a mean age of participants from 51 to 81 years who were predominantly male. However, there was evidence that more female and older participants had been recruited in recent trials since the 2010 review (Davies et al.). As with the 2010 review, there was evidence of high

levels of heterogeneity in the exercise-control difference in the MLHFQ scores at follow-up. Nevertheless, when data from the trials reporting total MLHFQ scores were pooled there was a clinically significant improvement with exercise training (MD -5.8; 95% CI -9.2 to -2.4; $p = 0.0007$, $I^2 = 70\%$; $\text{Chi}^2 = 40.24$, $p < 0.0001$, random-effects analysis) demonstrating the efficacy of aerobic exercise training, with or without resistance exercise, on QoL in CHF patients.

The HADS questionnaire and the MLHFQ were used in Study 4 (Chapter 5) to measure changes in QoL in CHF patients following an exercise training programme.

1.8 Conclusions and recommendations

Individual studies have produced conflicting results. When data are pooled in meta-analyses the results clearly demonstrate the efficacy of exercise-based rehabilitation by improvements in functional capacity (usually expressed as VO_2 peak), natriuretic peptides and health-related QoL in relatively young patients (often males) with stable CHF and few or no co-morbidities. It is evident that there are certain shortcomings that make the field worthy of further scrutiny. For example, previous investigations have used intensities of VO_2 peak and treadmill or cycle ergometer exercise training protocols; participants have been predominantly young males with few or no co-morbidities. Further scope for investigation lies in the mode and intensity of exercise, by selecting protocols that are routinely used by CR programmes in the UK, and in the population recruited.

1.9 Summary of aims and objectives of the studies within the thesis

The primary objective of the thesis was to assess the physiological and psychological effects of moderate intensity exercise training on patients with CHF and to provide new evidence examining the correlation between functional capacity, NT-proBNP levels and QoL following a 12-week course of supervised exercise. Participants randomised to an early intervention (EI) group commenced the exercise programme immediately following an initial assessment; participants in a delayed intervention (DI) group - the control group - were able to access the exercise programme following a second assessment at 12-weeks. Participants in the DI group received educational support from the Heart Failure Specialist Nurses but no formal exercise protocol; they were invited to continue their usual lifestyle. Two smaller studies were also designed to assess the validity and reliability of using a two-minute practice test prior to a 6MWT and of the Chester step test to assess HR, VO_2 and RPE responses in CHF patients. A third sub-group study examined the acute kinetics of NT-proBNP following a moderate intensity exercise session.

The following hypotheses have therefore been explored:

Study 1: a two-minute practice walk test provides adequate and appropriate preparation prior to performing a baseline 6MWT.

Study 2: a modified CST is a reliable and suitable sub-maximal alternative test of functional capacity in patients with CHF.

Study 3: NT-proBNP does not increase following a moderate intensity exercise session.

Study 4: In a representative sample of the UK CHF population, compared to that reported in the current evidence, and by applying current UK guidelines, a 12-week programme of exercise training:

- (i) Results in an improved functional capacity.

- (ii) Results in a reduction in plasma BNP levels and an associated improvement in LV function.
- (iii) Results in an improvement in QoL.
- (iv) Demonstrates a strong correlation between changes in functional capacity, with changes in plasma BNP levels and changes in QoL.

CHAPTER 2

General Methods

2.1 Method

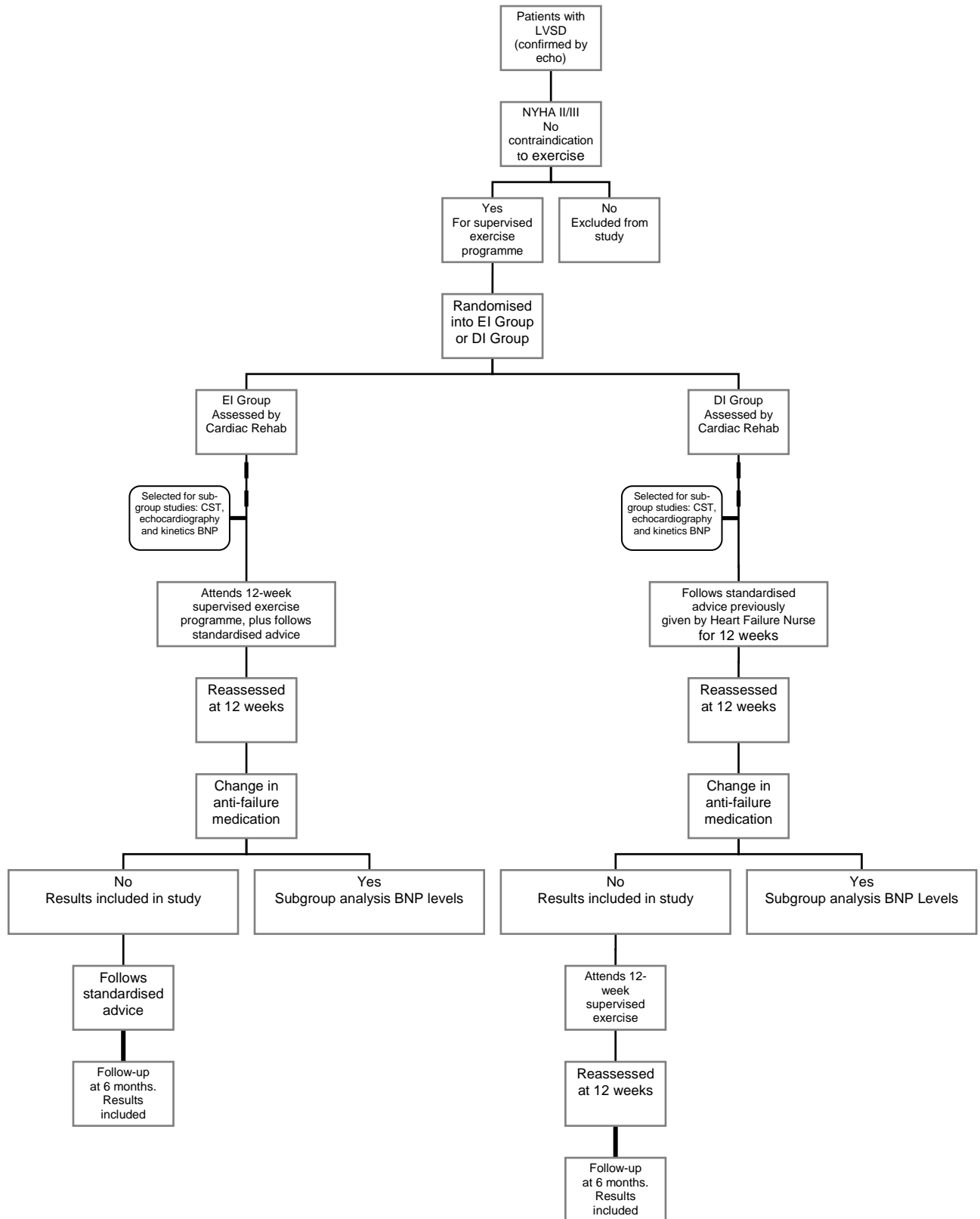
The following section aims to give an overview of a suite of studies on exercise-based rehabilitation that are encompassed within this thesis for patients attending a standardised CR programme at the Royal Wolverhampton NHS Trust's Heart and Lung Centre. This specialised programme is integral to an overall CR service that encompasses many cardiovascular conditions including IHD, Post-MI, Post-CABG and other related conditions including CVA and PVD.

All trials were incorporated into the standardised service where patients are referred to a 12-week programme, attending two sessions per week for supervised exercise training. The only change to routine practice to add validity to the study design was that some patients were deferred for 12 weeks, in a cross-over design, which allowed for an optimisation of a "control" group. This ensured that all eligible patients received rehabilitation as opposed to a more traditional non-interventional (placebo) control arm. The latter now being considered unethical in light of the modern acceptance that rehabilitation is a required part of CHF treatment (NICE, 2010).

Figure 2.1 provides an overview of the suite of studies that were encompassed within this thesis, followed by Method being applied through a number of these studies including:

1. Experimental Design
2. Participant recruitment
3. Planned sample size
4. Ethics, Good Clinical Practice and Approval
5. Consent

6. Randomisation
7. Pre-test screening
8. Testing Procedures and equipment
 - a. Resting measures and derived parameters: HR, BP and PP
 - b. Blood analyses: NT-proBNP
 - c. Exercise tests and protocol: Intensity, HR and RPE; 6MWT; exercise programming, prescription and progression
 - d. QoL



EI = Early intervention DI = Delayed intervention (control)

Figure 2.1 Study flow diagram

2.1.1 Experimental design

There was a small initial study prior to the main study, designed to assess the validity and reliability of using a two-minute practice test prior to a baseline 6MWT. During the main study several subgroups were selected to assess the following:

1. HR, VO_2 and RPE responses in CHF patients during an adapted Chester step test.
2. The kinetics of NT-proBNP following a moderate intensity exercise session.
3. Changes in LV function following a 12-week programme of moderate intensity exercise.

The main research (Study 4) was a parallel study, with a cross-over design, comparing outcome measures from a cohort of CHF patients who attended a 12-week supervised exercise programme (Early intervention; EI group) with outcome measures from a cohort of CHF patients who followed standardised advice from the Heart Failure Specialist Nurse (Delayed intervention; DI group) for 12 weeks. All patients had access to the exercise programme; however patients in the DI group had a delayed start in order to provide a control group (Table 2.1). The study used prospective data from both groups, over a 12 - month period. It used a repeated measures design, consisting of three main testing sessions: initial assessment/baseline (T1), 12-week follow-up (T2) and 6-month follow-up (T3) (Table 2.1). Patients in the DI group who went on to complete the exercise training programme had an additional assessment (T2b), at 24 weeks to examine specific outcome measures following the 12-week

programme. All testing was performed at the Royal Wolverhampton NHS Trust's CR Department at New Cross Hospital.

Table 2.1 Intervention details

Early Intervention Group	Delayed Intervention Group
<ul style="list-style-type: none"> a. Initial assessment (T1). b. Patients attend a 12-week course of supervised exercise in the Cardiac Rehabilitation Department at New Cross Hospital. c. Reassessment at week 12 (T2). d. Patients continue self-directed activities, following standardised advice. e. 6 month review (at week 36) (T3). 	<ul style="list-style-type: none"> a. Initial assessment (T1). b. Patients continue self-directed activities, following standardised advice. c. Reassessment at week 12 (T2). d. Patients attend a 12-week course of supervised exercise in the Cardiac Rehabilitation Department at New Cross Hospital. e. Reassessment at week 24 (T2b). f. 6 month review (at week 48) (T3).

2.1.2 Recruitment process

Patients diagnosed with left ventricular systolic dysfunction (LVSD) in Wolverhampton are seen by a Heart Failure Specialist Nurse for assessment, advice and education. Prescription of CHF medication and optimisation of beta-blocker and ACE inhibitor medication takes place in the Heart Review Clinic at the Royal Wolverhampton NHS Trust. Once stable on optimum medication patients are referred to a CHF CR exercise programme.

Participants were selected for this study by conforming to the following inclusion criteria:

- a. Referred to the CR exercise programme
- b. NYHA class II and III
- c. Stable CHF

- d. Anti-failure medication optimised
- e. Patient consent to joining the study

Participants were excluded from the study based on the following exclusion criteria:

- a. NYHA class I or IV
- b. Patient declines/withdraws consent
- c. Absolute contraindications to exercise

Eligible patients were invited to participate in the study and received further information, including the Patient Information Leaflet (Appendix 1 and 2) prior to consent. The patients were given a minimum of 24 hours to consider entry to the study and were free to discuss the study with relatives, friends and other health professionals if they wished. A screening log was kept of all patients approached for the study and whether they agreed to participate or not.

Sample Size

Due to the nature of this study, a convenience sample was used. The aim was to include at least 50 patients, with 25 in each Group. A service audit of clinical effectiveness (Leslie and Buckley, 2010) using a sample of 22 patients who had completed the CHF exercise programme showed that there was a trend towards a reduction in NT-proBNP levels following a 12 week course of exercise training ($p=0.075$). Patients who dropped out of treatment were invited to attend for follow-up assessment and these data are included in the analysis.

2.2 Ethics

2.2.1 Good Clinical Practice

All study procedures were in accordance with the recommendations guiding physicians in biomedical research involving human subjects, adopted by the 18th World Medical Assembly, Helsinki, Finland 1964, amended at Edinburgh in 2000. The trial was conducted in accordance with ICH GCP. There is no documented evidence to suggest that delaying the start of CR exercise training for CHF patients is in any way detrimental to their health.

2.2.2 Approval

Prior to commencing this study ethical approval was granted by NRES and Trust approval by The Research and Development (R&D) Directorate at the Royal Wolverhampton NHS Trust (Appendix 3 and 4). Further approval was granted following a Substantial Amendment to the study (Appendix 5 and 6), which included the addition of serial blood samples to examine the acute kinetics of NT-proBNP following moderate intensity exercise. Appropriate licensing for the use of the MLHFQ was granted by the University of Minnesota.

2.2.3 Data monitoring

Data was monitored for completeness and quality by the R&D Directorate via the Quality Assurance process.

2.2.4 Confidentiality

The research complies with all aspects of the Data Protection Act 1998. Any information which would allow individual patients or clinicians to be identified will not be released.

2.2.5 Consent

Informed consent discussions and a pre-assessment screen took place prior to the initial assessment (T1), where patients were encouraged to ask questions before giving consent and being entered in the study. Written informed consent was obtained prior to randomisation and initial assessment by the patient completing the consent form (Appendix 7 and 8). A copy of the consent form was offered to the patient, and copies of this form and the Patient Information Leaflet were kept in the patient's CR treatment record. To ensure participant confidentiality all participants were allocated a unique identification number.

2.2.6 Randomisation

Sequentially, following consent, participants were randomised into the EI group or the DI group, for practical pragmatic reasons in an attempt to avoid disproportionate group sizes (resource and Health & Safety issues in respect to class size).

2.3 Test procedures and equipment

Participants were tested in their usual CR clinics therefore reducing the potential stress of attending a hospital environment for the study and also not adding any extra journeys for the participants in the study.

2.3.1 Resting measures/pre-test screen at T1

On arrival at the CR clinic, patients were asked to sit on a chair and rest for 10 minutes, to ensure a more accurate resting heart rate (RHR) was achieved prior to the test commencing. During this seated period during T1 participants were required to complete the informed consent form and a pre- test health screen was undertaken. The findings of the health screen ensured that participants were suitable to participate in the study, namely by taking their prescribed medications and not having any absolute contraindications to exercise. At all assessments, after the 10 minute rest period, participants RHR was taken through a radial pulse check for 15 seconds which also allowed for basic screening of any potential arrhythmia. Blood pressure was checked using an automated sphygmomanometer on the participants left arm, unless there was a clinical reason as to why the left arm could not be used.

Exercise training guidelines for patients with CHF set by the Association of Chartered Physiotherapists in Cardiac Rehabilitation (ACPICR) (2009) recommend a training HR range between 40% and 60% of HRR in order to prescribe safe and effective exercise for patients with CHF. HR is a commonly used measure of exercise response due to ease of monitoring plus its direct relationship with VO_2 max; VO_2 max being plausibly predicted from sub-maximal exercise (Johnson and Siegel, 1981). HRR allows for a more accurate relationship between % HR max and VO_2 max as it considers the influence of varied resting HRs (Karvonen et al., 1957). If the exact HR max is not known (i.e. from a maximal exercise tolerance test) then the 220 – age method is often used, for which the accuracy has been questioned (Robergs and Landwehr,

2002). This is particularly relevant for CHF patients due to the prescription of beta-blockers and the incidence of chronotropic incompetence. Beta-blockers are known to reduce both RHR and HR during exercise by as much as 20 – 30% (Head, 1999). Chronotropic incompetence has been defined as the inability of the heart to increase its rate commensurate with increased activity or demand, and failure to achieve at least 80% of maximum HR or HRR during an incremental exercise test or inadequate submaximal HR are examples of impaired chronotropic response (Brubaker et al., 2011). The underlying mechanisms are yet to be completely understood. Wosnich et al. (2003) reported a mean resting HR 15 ± 5 beat. min⁻¹ lower in a small cohort of beta-blocked healthy males compared to a placebo group ($p < 0.05$). Mean HR was also significantly lower at aerobic threshold (-19 ± 8 beat. min⁻¹), anaerobic threshold (-22 ± 10 beat. min⁻¹) and maximal workload (-19 ± 11 beat. min⁻¹) with bisoprolol compared to placebo. Percentage of HRmax was significantly reduced at rest aerobic threshold (64% vs 60%) and anaerobic threshold (86% vs 82%). The authors recommended the use of RPE to prescribe exercise for patients taking beta-blockers. Tabet et al. (2006) later proposed that a modified formula should be available for beta-blocked patients. A specialised equation for estimating maximum HR in CHF has since been developed by Keteyian et al. (2012).

Predicted maximum HR was therefore calculated using the equation by Keteyian et al. (2012):

$$119 + 0.5(\text{RHR}) - 0.5(\text{age})$$

Sixty percent of HR reserve (HRR) was then calculated as a test termination point; this percentage generally corresponds with the first ventilatory threshold (Beale et al., 2010). The equation $220 - \text{age}$ has been shown to over-estimate measure maximal HR in patients taking beta-blockade therapy, with a prediction error of 40 ± 19 beats (Keteyian et al, 2012). Keteyian et al. (2012) used data from 767 participants enrolled in the HF-ACTION trial to validate a more appropriate equation that used both age and RHR to predict maximum HR in patients with CHF taking beta-blockers. The authors considered the above equation was helpful with evaluation of chronotropic response, but advised that the magnitude of the variation (standard error of the estimate = $18 \text{ beat} \cdot \text{min}^{-1}$) may render it impractical when prescribing intensity. It is noteworthy that the cohort of 767 patients was in sinus rhythm (i.e. no pacemaker and no atrial fibrillation) thus the results may not be generalisable to all patients with CHF.

Present at all assessment sessions was another member of the CR team or a student physiotherapist, trained in immediate life support.

2.3.2 Pulse pressure

Pulse pressure (PP) was calculated pre-exercise and at end of exercise test from the difference of the measured systolic and diastolic blood pressures (Blacher and Safar, 2005) using the following formula:

$$PP = P_{\text{systolic}} - P_{\text{diastolic}}$$

2.3.3 Plasma NT-proBNP levels

Blood was sampled using a polyethylene cannula placed in an antecubital vein in the left or right arm by a trained Research Nurse and collected into an EDTA (anticoagulant) sampling tube. Blood samples were collected after the initial pre-screening and prior to the 6MWT. The blood samples were transferred to the hospital's Clinical Chemistry laboratory and were centrifuged by a laboratory technician at 3200rpm for 3 minutes in a Centrifuge Megafuge II. Plasma was then separated and immediately aliquoted into labelled cryo-vials and frozen at -80°C until analysis. NT-pro-BNP was measured in batches using a commercially available electrochemiluminescence immunoassay based on a polyclonal antibody-based sandwich chemiluminescence assay (Roche Diagnostics) using an autoanalyser. Although BNP levels do not appear to rise and fall in any circadian rhythm (Jensen et al., 1997), samples were obtained at the same time of day to reduce any possibility of diurnal variation.

2.3.4 Rating of perceived exertion

A rating of perceived exertion (RPE) can complement HR during exercise testing and has been recognised as a marker of physiological intensity (Buckley et al., 1999); RPE is frequently used to assess fitness, guide exercise prescription and monitor safe and effective levels of exercise/activity (Buckley and Eston, 2007) as it allows patients to monitor feelings of exercise intensity, which in turn allows them to pace themselves accordingly. The reliability of Borg's 6 – 20 RPE scale (Borg, 1998) has been confirmed by Buckley et al. (2009). An RPE of 14/15 corresponds to 80% HR max and is therefore

considered a reasonable, albeit subjective, end point to a sub-maximal exercise test (Buckley et al., 2004). However, Eston and Thompson (1997) reported that patients with CHD tend to overestimate exercise intensity compared to healthy controls. In contrast, Joo et al. (2004) concluded that a self-reported RPE of 11–13 in 11 patients with CHD may result in exercise intensity levels that are inappropriately high for exercise-based CR, and recommended being aware of the effects of beta-blockers on local and overall RPE with respect to the cardioselectivity. These conflicting findings may be the result of different cardioselectivity of beta-blockers (Eston and Connolly 1996). Cardioselective beta-blockers such as bisoprolol do not seem to have as pronounced effects on the RPE response compared to non-cardioselective betablockers, such as carvedilol. Therefore, the authors concluded that RPE can be used to determine exercise intensity in patients taking cardioselective beta-blockers. Before starting exercise testing participants were presented with the 6 – 20 RPE scale (Borg, 1998).

Standardised instructions, specific to using the RPE scale (Figure 2.2) in estimation mode were given:

- (i) The top and bottom ratings were anchored to previous experience of no exertion at all and maximal effort.
- (ii) Patients were instructed to give an over all rating of the exertion incorporating physical, muscular and cardiorespiratory sensations.
- (iii) They were advised that there was no right or wrong answer.
- (iv) Verbal descriptors as well as the numerical values were used.
- (v) The scale was on view at all times throughout the test so that patients could report their RPE at any time to ensure their comfort.

The exercise test was stopped if any of the following were reported:

- a. Chest Pain
- b. Intolerable shortness of breath
- c. Dizziness, pallor and diaphoresis
- d. Participant requested the test to be terminated
- e. RPE ≥ 14 on the Borg scale

6	No exertion at all
7	
8	Extremely light
9	Very light
10	
11	Light
12	
13	Somewhat hard
14	
15	Hard (heavy)
16	
17	Very hard
18	
19	Extremely hard
20	Maximal exertion

Figure 2.2 Rating of perceived exertion (Borg, 1998)

2.3.5 Functional exercise capacity: Sub-maximal exercise test

Prior to the sub-maximal exercise tolerance test commencing participants were fitted with a pulse oximeter to allow HR to be monitored. After validating the use of a two-minute practice walk (Study 1, Chapter 3a), this was used prior to the baseline 6MWT; the protocol is detailed below. HR and distance were recorded at the end of each minute of the walk tests in order to calculate the heart-rate-walking speed index (Buckley et al., 2010). This was calculated by dividing the total number of heart beats by walking distance attained during the test and multiplied by 10 to describe heart beats per 10 m walked.

2.3.5.1 Walk test protocols

The 2MWT and the 6MWT were conducted using a standardised approach. A 20 metre course was marked in a level CR Gymnasium, with chairs placed every 5 metres. Before performing the practice test, patients were presented with the 6 – 20 RPE scale (Borg, 1998). Standardised instructions regarding RPE (Figure 2.1) were given before each participant began walking. The area is one that is seldom travelled to avoid disruption. The turnaround points were clearly marked with cones. A starting line which marked the beginning and end of each lap was marked on one of the cones. The test protocol is based on the American Thoracic Society guidelines (2002), which provide a standardised approach for performing the test.

Required Equipment

- a. A stopwatch
- b. A lap counter
- c. Small cones to mark the turnaround points
- d. Chairs located along the walking course
- e. A clipboard for paperwork
- f. Access to emergency equipment and a telephone
- g. An electronic blood pressure machine
- h. A pulse oximeter
- i. A Borg Scale of Perceived Exertion (Borg, 1998)

Patient Preparation

- a. Patients were advised to wear comfortable clothing, with appropriate footwear for walking
- b. Patients could use their normal walking aids during the test
- c. The patients were advised to continue to take their normal medication
- d. Patients were asked to avoid eating a meal one hour prior to the test
- e. Patients were advised not have exercised vigorously within 2 hours of the test
- f. Blood samples for testing BNP levels were obtained prior to testing

Measurements

A portable pulse oximeter (Nonin Onyx II 9550 %SpO₂ digital fingertip pulse oximeter) was used to measure and record baseline heart rate. Pulse irregularity was noted before starting the test by a manual check. The pulse oximeter was lightweight, battery powered and held in place so that the patient did not have to hold or stabilise it and was worn throughout the walk.

The patient was asked to stand and rate their baseline dyspnoea and overall fatigue using the Borg Scale (Borg, 1998). The lap counter was set to zero and the timer to 6 minutes, and the patient moved to the starting point

The patient was instructed as follows:

“The object of the test is to walk as far as possible for 6 (or 2 if undertaking two-minute practice test) minutes. You will walk around these cones. Six minutes is a long time to walk, so you will be exerting yourself. You will probably get out of breath or become tired. You can slow down, or stop and rest as necessary, but you should resume walking as soon as you are able.

You will be walking around the cones. You should move quickly around the cones and continue without hesitation (demonstrate by walking one lap; walk and pivot around the cones briskly).

I am going to use this counter to keep track of the number of laps you complete. I will click each time you turn around at this starting line. Remember that the object is to walk as far as possible in 2/6 minutes, but don't try to run or jog.

Start now."

1. The patient was positioned at the starting line. As soon as the patient started to walk, the timer was started.
2. The patient was not spoken to during the test other than using standard phrases of encouragement. Each time the patient returned to the starting line, the lap counter was clicked once
3. Heart rate and rating of perceived exertion were checked at the end of each minute and recorded, along with the distance walked and any reported symptoms, on the treatment card. At the end of each minute the patient was informed that they were doing well and that they had x minutes to go. If the patient needed to stop and rest during the test, they were reminded to continue to walk as soon as they were able. The timer was not paused during rest periods. If the patient stopped before the 2 or 6 minutes end point and refused to continue/it was considered inappropriate for them to continue the test was discontinued. The distance, the time stopped and the reason for stopping prematurely was recorded on the treatment record.
4. When the timer was 15 seconds from completion, the patient was advised:

"In a moment I am going to tell you to stop. When I do, just stop where you are and I will come to you."

5. When the timer rang, the patient was asked to stop. HR, blood pressure and RPE were recorded at the end of the test.
6. The patient was congratulated and offered a drink of water.

Variability

Sources of variability caused by the test procedure were controlled as much as possible by following the protocol above. Repeat testing was performed at a similar time of day to minimise intraday variability.

Practice Tests

A practice test is not needed in most clinical settings, but is recommended when undertaking research studies. The baseline 6MWT was performed 20 minutes after the practice test (2MWT).

Encouragement

Only the standardised phrases below were used during the test:

At the end of each minute: "You are doing well. You have x minutes to go."

When a patient stopped to rest: "Continue walking whenever you feel able to."

When the timer was 15 seconds from completion: "In a moment I am going to tell you to stop. When I do this, just stop right where you are and I will come over to you."

When the timer rang: "Stop!"

Interpretation

Total distance walked was recorded for all tests performed, and changes expressed as an absolute value. Total distance walked was also expressed as an estimated MET value by calculating the average pace per minute. Distance, HR and RPE were recorded at the end of each minute for heart rate-work rate comparison.

2.3.6 Quality of life

The New York Heart Association (NYHA) classification stratifies patients according to physical activity/exercise limitation (Table 2.2). It was used in this study to provide a subjective measure of disability, although it has a limited relation to objective measures of exercise capacity (Lainchbury and Richards, 2002). The QoL questionnaires were administered after completion of the 6MWT. If a patient presented a limitation in completing the questionnaires, such as difficulty reading, the health professional offered assistance. The instructions at the top of the HADS questionnaire (Appendix 9) were read out to the patient and the health professionals encouraged the patients to choose answers based on symptoms they had experienced during the previous week and asked them to provide spontaneous answers without excessive reflection. The MLHFQ (Appendix 10) was then administered. The instructions at the top of the questionnaire were read out to the patient and they were asked to circle the 0, 1, 2, 3, 4 or 5 to indicate how much their life was affected by their condition. If a question did not apply to them, they were asked to circle the 0 after that question. The National Audit for Cardiac Rehabilitation Physical Activity questionnaire (Appendix 11) was used to assess patient exercise/activity levels. Patients self-reported the number of occasions during a seven-day period that they had carried out strenuous, moderate or low intensity activity for a duration in excess of 15 minutes, and indicated whether they were currently taking regular physical activity on average 5 times a week active for 30 minutes. Blood pressure and HR were checked again prior to the participant leaving the department, to ensure that they had returned to baseline levels.

Table 2.2 New York Heart Association classification

I	No limitation of activity
II	Slight limitation of activity
III	Marked limitation of activity
IV	Inability to carry out activity

2.4 Exercise training protocol

The training programme followed guidelines of the British Association for Cardiovascular Prevention and Rehabilitation (BACPR) (2012) and the Association of Chartered Physiotherapists in Cardiac Rehabilitation (ACPICR) (2009). Participants attended supervised exercise training sessions twice a week for 12 weeks, with an Exercise Physiologist, student physiotherapist and a Heart Failure Specialist Nurse present at each session. Sessions consisted of a 10 to 15 minute warm up, 22 minutes moderate intensity aerobic exercise and low intensity resistance/active recovery exercises (Appendix 12). Intensity was set in accordance with the ACPICR (2009), using a target HR of 40 – 60% of HRR and/or RPE of 12-13 on Borg's scale. HR is routinely used for exercise prescription due to the existing linear relationship between HR and VO_2 and the use of RPE scales is based on the findings that demonstrate that strain perception increases linearly with exercise intensity (Carvalho and Mezzani, 2011). Borg scale RPE values between 11 and 13 are reliable for exercise training prescription in CHF patients on beta-blockers, assuring an energy expenditure lying between the first and second ventilatory thresholds (Carvalho et al., 2009). Furthermore, with the high incidence of atrial fibrillation in this

population the RPE scale is particularly useful as the HR versus intensity relationship may be affected. These levels were also recorded in relation to an estimated MET level determined from the initial 6MWT. Over the 12 weeks, the exercise programme was progressed on the basis of increasing the level of work to always attain these levels. A 10-minute cool down period completed the exercise session, followed by relaxation activities and education. Blood pressure and HR were measured before each session; HR and RPE were monitored during the exercise session, with a final HR check following relaxation. Valid consent was obtained from the patient prior to each exercise session.

In addition to supervised sessions, participants were also asked to undertake exercise/physical activity of moderate intensity for 30 minutes on at least three days of the week. On completion of the 12-week course participants attended for a re-assessment as detailed above (T2 and T2b), with a further assessment 6 months later (T3).

CHAPTER 3

The use of walking and step tests in heart failure
rehabilitation

Overview:

Exercise intensity should be prescribed from an appropriate assessment. The gold standard method is an incremental cardiopulmonary exercise test (CPET) with respiratory gas analysis, which directly measures VO_2 at the first and second ventilatory thresholds and peak VO_2 (Carvalho and Mezzani, 2011). However, in routine clinical practice CPET is seldom available, particularly for CHF patients. Sub-maximal tests using HR and RPE as descriptors of energy expenditure are therefore used.

In this chapter two tests (a practice test prior to a 6MWT and an adapted Chester step test) have been evaluated and adapted for use in CHF populations; the aim being to make adaptations to current protocols that can enhance their reliability, validity and practicality of use for outpatient clinical settings (hospital, community or home venues). Study 1 evaluated the two-minute walk test (2MWT) as a practice test prior to a 6MWT and Study 2 an adapted Chester step test (CST).

3a, Study 1

Do patients with chronic heart failure
need a full six-minute practice test?

Aspects of this chapter were presented at the British Cardiovascular Society
Annual Conference July 2013 (see Appendix 13)

3.1 Abstract

Background: The 6MWT is a useful measure of functional capacity for people with moderate to severe cardiorespiratory impairment (e.g. chronic heart failure; CHF). A practice 6MWT test is recommended in both clinical practice and research to increase the reliability of the test by aiming to filter out influences of familiarisation, pacing and motivation on final outcome tests. The effects of fatigue from a full six-minute practice test are also of practical concern in influencing 6MWT results.

Objective: The aims of this small study were to examine the efficacy of a two minute practice walk test in predicting 6MWD, whilst providing enough familiarisation in patients with CHF and to assess the efficacy of a two-minute versus a six-minute practice test on pacing and possible fatigue during a subsequent 6MWT.

Methods: Twenty patients diagnosed with CHF (55% following myocardial infarction) were recruited. All patients were stable on optimal medical therapy for at least four weeks; all had exertional dyspnoea, fatigue or both and were classified according to NYHA functional class II to III. Patients were allocated into two groups. Group 1 (n = 10; 9 male) performed a two-minute self-paced practice walk test (Grp1-2min), had a 20 minute rest, followed by a 6MWT. Group 2 (n = 10; 7 male) performed a full six-minute practice test (Grp2-6min), had 20 minutes rest, followed by a 6MWT. Heart rate (HR) and ratings of perceived exertion (RPE) were monitored throughout all tests.

Results: Practice and baseline 6MWT distance in Grp2-6min were the same (404 ± 94 m vs 424 ± 81 ; $p = .123$). Actual baseline 6MWT distance walked in Grp1-2min was not significantly different (345 ± 83 m vs 329 ± 96 ; $p = .212$) to the distance extrapolated from the mean distance walked during the two minute practice (115 ± 28 m). Effects of pacing or fatigue on walking pace were assessed between practice and baseline 6MWT using a bias \pm 95% limits of agreement (LoA) analysis. There was no difference ($p = .823$) in walking pace during the two-minute practice test (57.5 ± 3.8 m.min⁻¹) and the baseline 6MWT (57.8 ± 14.7 m.min⁻¹). Although walking paces were different ($p = .042$) between Grp1-2min (56.1 ± 16.1 m.min⁻¹) and Grp2-6min (70.6 ± 13.6 m.min⁻¹) in the baseline tests their respective mean heart rate (HR), % heart rate reserve

(HRR), heart-rate-walking speed index (HRWSI) and rating of perceived exertion (RPE) were the same: HR 103 ± 10 beat.min⁻¹ vs 99 ± 11 beat.min⁻¹ ($p = .360$); %HRR $65 \pm 28\%$ vs $60 \pm 14\%$ ($p = .684$); HRWSI 19.4 ± 7.9 vs 14.2 ± 3.1 beats per 10 m walked ($p = .068$) and RPE 12.7 ± 1.2 vs $11.7 \pm .8$ ($p = .052$). Comparison of the HRWSI also provides further evidence around reliability of a two-minute practice walk.

Conclusions: A two-minute practice test was as good as a full six-minute practice test in predicting baseline 6MWD in this cohort of patients with CHF. This demonstrates that a two-minute practice test can be used equally as well but saves valuable clinical assessment time (and thus costs). Furthermore a two-minute practice may reduce subsequent fatigue (in some low functioning patients) during the baseline 6MWT. Ideally a third trial, either on the same day or on another day within one week would have added further confirmation to whether a two-minute test does suitably achieve the same “reliability” improvements as a full six-minute practice test. Comparison of HRWSI provides further evidence for demonstrating the reliability effects of a two-minute practice test.

3.2 Introduction

The 6MWT is a popular and useful clinical measure of functional capacity, aimed particularly at people with moderately severe impairment (ATS, 2002; Enright, 2003); thus increased six-minute walk test distance is used routinely as an outcome measure for chronic heart failure (CHF)-rehabilitation (Guazzi et al., 2009). Patients with CHF are restricted by shortness of breath or fatigue during exercise. Breathlessness is frequently the prominent symptom during rapidly incremental protocols, and fatigue often occurs during gradually incremented tests (Tavazzi et al., 2001). The 6MWT therefore gives a more accurate representation of the ability of patients with CHF to perform sub-maximal activities of daily living due to the self-selected pace/intensity and the ability to include breaks to rest (Riley et al., 1992).

The 6MWT is considered a sub-maximal exercise test due to execution time, simplicity and greater acceptance by patients (Faggiano et al, 2004). However, Kosak and Smith (2005) suggested that the 6MWT may induce significant fatigue and the need for rest stops in patients with COPD, thereby being a better measure of endurance. Two further studies have demonstrated that fatigue occurs during a 6MWT in patients with spinal muscular atrophy (Montes et al., 2010) and polio (Skough Vreede et al., 2013).

In 1997 Faggiano et al. showed that oxygen uptake (VO_2) during a 6MWT was on average only 15% lower than peak VO_2 during a symptom-limited cardiopulmonary exercise test. Seven (27%) of 26 CHF patients in the study exercised on a predominantly anaerobic metabolism and showed a 6MWT VO_2 equal to or higher than peak VO_2 . Consequently, the 6MWT appears to have

features of both a sub-maximal test and a maximal test and could therefore be used to assess the maximal functional capacity in some patients with heart failure, particularly those with more severe CHF and severely limited exercise capacity. Guimarães et al. (2008) also reported that the 6MWT could actually demand a high level of exercise intensity from the patient, expressed by a respiratory quotient >1.0 . Thus standardizing the 6MWT and using the Borg scale to guide walking pace was proposed to ensure that patients undergo a sub-maximal walking test.

Both in clinical practice and in research when using the 6MWT in CHF, a practice test is recommended to increase the reliability of the test by filtering out the influences of familiarisation on final outcome tests, as discussed in Chapter 1. Current recommendations suggest that patients need to perform a full practice test, but there is concern that this may induce the need for rest stops. The 2MWT is considered a valid and time-efficient measure of self-paced walking speed, less hampered by fatigue than longer walking tests (see Chapter 1).

The aim of this study was to examine the efficacy of a two minute practice walk test as a time and cost-saving alternative compared to the recommended six-minute practice test, used to familiarise patients with CHF in order to ensure the reporting of reliable outcomes compared to baseline. The following hypothesis was explored: a two-minute practice walk test provides adequate and appropriate preparation prior to performing a baseline 6MWT.

3.3 Methods

3.3.1 Participants

A subgroup of the larger intervention study (Study 4, Chapter 5) of 20 patients, diagnosed with CHF was recruited to this study. All patients were referred to a hospital-based CR exercise training programme. Participants were stable on optimal medical therapy for at least four weeks and had exertional dyspnoea, fatigue or both and were classified according to NYHA functional class II to III. See Chapter 2 for details of recruitment, Hospital Trust and Regional Ethical approval, Patient Information and consent.

3.3.2 Procedures

Prior to starting the exercise programme participants were randomly allocated into two groups. Participants in group 1 (Grp1-2min; n = 10; 9 male) underwent a self-paced two-minute practice walk test, followed by 20 minutes rest before performing their baseline 6MWT. Patients in group 2 (Grp2-6min; n = 10; 7 male) underwent a self-paced practice 6MWT, followed by 20 minutes rest before performing their baseline 6MWT. Heart rate (HR) and ratings of perceived exertion (RPE) were monitored throughout all tests and were recorded each minute. Blood pressure (BP) was measured pre and post testing. Heart rate reserve (HRR) was calculated using the methods described in Chapter 2. Distance walked each minute and total 2MWT distance and 6MWT distance were recorded. 6MWT distance was then used to calculate the walking pace. HRWSI was calculated using the methods described in Chapter 2.

3.3.3 Walk test protocol

See General Methods, Chapter 2. Standardised instructions, information and verbal encouragement were given by the experienced CR Exercise Practitioner (a Specialist Physiotherapist or a Senior Exercise Physiologist) throughout all walk tests in order to address the problem of reproducibility.

3.3.4 Data analysis

Data were assessed for the normality of their distributions via the Shapiro-Wilk prior to analysis. The t-test for independent samples analysed differences in between-group baseline characteristics. Following analysis using a factorial (mixed) two way Analysis of Variance (ANOVA), between-group differences in HR, %HRR walking distance and pace were tested using t-test for independent samples. Within-subjects differences were analysed using the t-test for related samples (paired t-test); the Mann Whitney U test was used to measure between-group differences in RPE and the Wilcoxon signed ranks test for within-subjects differences. The 6MWT distance extrapolated from the two minute practice walk distance and the actual baseline 6MWT distance were also compared using the t-test for related samples (paired t-test), and the Pearson Correlation assessed the relationship between the practice 2MWT distance and the baseline 6MWT distance in Grp1-2min. Effects of pacing or fatigue on walking pace were further assessed between practice and baseline 6MWT using a bias \pm 95% limits of agreement (LoA) analysis using the equation: mean difference \pm 1.96(standard deviation), as recommended by Buckley (2011) when measuring reliability in exercise tests. Data analysis was conducted using SPSS version 21.0 and alpha was set at the .05 level.

3.4 Results

Twenty participants (mean age 69 ± 11 years; 16 male), all prescribed beta-blockade medication, completed the testing. Table 3.1 summarises patient baseline characteristics.

Walk distance: Participants in Grp1-2min walked between 55m – 160m during the two minute practice walk test; in Grp2-6min participants walked between 270m – 550m during the practice 6MWT. Baseline 6MWT distance for Grp1-2min ranged between 155 m and 495 m and Grp2-6min between 310 m and 585 m. Practice and baseline 6MWT distance in Grp2-6min were the same (404 ± 94 m vs 424 ± 81 ; $p = .123$). Mean walking performance data for distance and pace are summarised in Table 3.2.

The predicted 6MWT distance in Grp1-2min, calculated from the mean distance walked during the two-minute practice (115 ± 28 m), was extrapolated to 345 ± 83 m in 6 minutes. The actual baseline distance walked in this group was not different (329 ± 96 ; $p = .212$) to the predicted distance.

Table 3.1 Patient baseline characteristics

	Grp1-2min	Grp2-6min	p value
Mean age (years)	73 ± 10	65 ± 12	.066
Male/female (n)	9/1	7/3	
Body mass index (kg/m ²)	30.7 ± 3.9	31.1 ± 3.0	.436
CHF cause: idiopathic/ischaemic (n)	4/6	4/6	
Left ventricular ejection fraction (%)	34 ± 7	33 ± 9	.774
NYHA class II/III (n)	5/5	8/2	
Resting heart rate (beat. min ⁻¹)	76 ± 11	66 ± 18	.295

Walk pace

There was a significant high correlation between the two-minute practice test and the baseline 6MWT in pace ($r = .945$; $p = .0001$) and in distance ($r = .924$; $p = .0001$) in Grp1-2min. There were no significant between-group differences in walking pace at two minutes during the practice tests ($p < .122$). However, during the baseline tests there were significant differences in pace (Table 3.2). Walking pace at minute 2 of the practice and the baseline tests were the same in Grp1-2min ($p = .823$) but were different in Grp2-6min, who walked significantly faster in the baseline test compared with the practice test ($68.3 \pm 15.7 \text{ m.min}^{-1}$ vs $72.0 \pm 13.7 \text{ m.min}^{-1}$; $p = .007$). However, pace at minute 6 of the practice walk and the baseline test were the same in Grp2-6min ($67.3 \pm 15.6 \text{ m.min}^{-1}$ vs $70.6 \pm 13.6 \text{ m.min}^{-1}$; $p = .123$). Walking pace at minutes 2 and 6 of the baseline test were also the same in Grp1-2min ($p = .300$). The mean difference at minute 2 in Grp1-2min was $.250 \text{ m.min}^{-1}$ with the 95% LoA being

-6.97 to 6.47 m.min⁻¹; between minutes 2 and 6 of the baseline test the mean difference was -1.68 m.min⁻¹ with the 95% LoA being -11.14 to 7.78 m.min⁻¹. In Grp2-6min the mean difference at minute 6 was 3.4 m.min⁻¹ with the 95% LoA being -15.5 to 8.82 m.min⁻¹.

Heart rate and ratings of perceived exertion

Although there was a significant difference between the two groups in walking distance achieved ($p = .028$) and thus walking speed ($p = .038$) during the baseline 6MWT (Table 3.2) both groups were performing at the same relative exercise intensities as noted by the similar HRs, %HRR and RPEs:

- HR at minute 2: Grp1-2min = 95 ± 9 beat. min⁻¹, Grp2-6min = 92 ± 9 beat.min⁻¹; $p = .461$
- HR at minute 6: Grp1-2min = 103 ± 10 beat.min⁻¹, Grp2-6min = 99 ± 11 beat.min⁻¹; $p = .360$
- %HRR at minute 2: Grp1-2min = $44 \pm 29\%$, Grp2-6min = $46 \pm 15\%$; $p = .865$
- %HRR at minute 6: Grp1-2min = $65 \pm 28\%$, Grp2-6min = $60 \pm 14\%$; $p = .684$.

In Grp1-2min there were significant differences in the end of test RPEs between the practice test and the baseline test, and between RPE at minute 2 and minute 6 in the baseline 6MWT (Table 3.3). RPE at minute 2 of the practice and the baseline tests were the same in both groups (Table 3.3, $p = 1.0$), as were the RPEs in minutes 2 and 6 in the baseline 6MWT for Grp2-6min ($11.2 \pm .8$ vs $11.7 \pm .8$; $p = .258$).

Table 3.2 Walking distances (SD) and paces (SD) of a six-minute walk test (6MWT) preceded by a two-minute or a six-minute practice test in CHF patients

Group	Practice distance walked (m)	Baseline 6MWT distance (m)	Practice test walk pace at 2 mins (m.min ⁻¹)	Baseline 6MWT walk pace at 2 mins (m.min ⁻¹)	Baseline 6MWT walk pace at 6 mins (m.min ⁻¹)
1 (Two minute practice)	115 (28)	329 (96)	57.5 (13.8)	57.8 (14.7) [‡]	56.1 (16.1) ²
2 (Six minute practice)	404 (94)	*424 (81) [‡]	68.3 (15.7)	**72.0 (13.7) ¹	***70.6 (13.6) ³

* Significantly greater walking distance than Group 1 ($p = .028$)

**Significantly faster walking pace than Group 1 ($p = .038$)

*** Significantly faster walking pace than Group 1 ($p = .042$)

[‡] Not significantly different from the practice test

¹Significantly faster walking pace than practice test at minute 2 ($p = .007$)

²Not significantly different from minute 2

³Significantly slower walking pace than that at minute 2 ($p = .040$)

Table 3.3 Mean RPE (SD) at minutes 2 and 6 in the practice test and the baseline test

	RPE at 2-minutes practice test	RPE at 2-minutes in baseline 6MWT	RPE at 6-minutes in baseline 6MWT
Group 1	*11.5 (1.3)	11.5 (.9)**	*12.7 (1.2)**
Group 2	11.2 (.4)	11.2 (.8)	11.7 (.8)

* Significant difference between practice test minute 2 and baseline minute 6 ($p = .046$)

** Significant difference between baseline minute 2 and baseline minute 6 ($p = .026$)

Heart-rate-walking speed index

Participants in Grp1-2min had a mean HRWSI during the practice test of 17.6 ± 6.3 and 19.4 ± 7.9 at baseline ($p = .127$). In Grp2-6min the HRWSI during the

practice test was 15.1 ± 3.9 , and at baseline 14.2 ± 3.1 beats per 10m walked ($p = .202$). HRWSI was the same in both groups during the practice walk ($p = .314$) and during the baseline 6MWT ($p = .068$).

3.5 Discussion

The key findings in this study are that the 6MWT distance extrapolated from the two-minute practice walk in Grp1-2min was not significantly different to the actual baseline distance that they walked (predicted: 345 ± 83 m vs actual: 329 ± 96 m; $p = .212$). In this cohort regression analysis was not deemed necessary to calculate predicted 6MWT performance from the practice 2MWT as speed stayed constant (Table 3.3) across practice and baseline tests. From the perspective of performance (walking speed), the presence of significant fatigue caused by a practice test could not be shown (practice 2MWT pace 57.5 ± 13.8 m.min⁻¹ vs baseline 6MWT pace 56.1 ± 16.1 m.min⁻¹; $p = .823$). However, based on the RPE, it could be postulated that a greater RPE at the end of the 6MWT compared to the 2MWT practice was a sign of fatigue. Kosak and Smith (2005) hypothesised that the overestimation of 6MWD was due to the effects of fatigue during the longer test. The small but significant difference in end of test RPEs were 11.5 ± 1.3 vs 12.7 ± 1.2 ; $p = .046$. These results reflect the end of test RPE scores reported by Leung et al. (2006) in their study of 45 patients with COPD (mean modified Borg Scale RPE in 2MWT 3.0 ± 2.0 , in 6MWT $3.3 \pm .3$; $p < .05$) and support the hypothesis that CHF patients being required to perform a full six-minute practice walk may actually cause fatigue in the follow-up 6MWT in many of the patients; thereby affecting “test performance” of Grp1-

2min. In contrast Grp2-6min reported the same RPE at minutes 2 and 6 of the baseline test ($11.2 \pm .8$ vs $11.7 \pm .8$; $p = .258$). But although the baseline RPEs were the same, the actual walking pace reduced from minute 2 to minute 6 in Grp2-6min (from 72.0 ± 13.7 m.min⁻¹ to 70.6 ± 13.6 m.min⁻¹; $p = .040$) suggesting an element of fatigue. Montes et al. (2010) also reported that the mean distances walked during the first minute (57.5 m) and the sixth minute (48.0 m) of a 6MWT were considerably different ($p = .0003$) in 18 participants with spinal muscular atrophy, observing a mean velocity decrease for each successive minute walked. Skough Vreede et al. (2013) investigated 18 patients with post-polio syndrome and also found a 14% decrease ($p < .001$) in walking pace from the beginning to the end of the 6MWT.

Although mean baseline 6MWT distance in Grp2-6min was higher than the practice 6MWT distance, there was no clinically significant (see Chapter 1) or statistically significant difference (practice: 404 ± 94 m vs baseline: 424 ± 81 ; $p = .123$). Grp2-6min walked a significantly greater distance in the baseline 6MWT than Grp1-2min (Grp2-6min: 424 ± 81 m vs Grp1-2min: 329 ± 96 m; $p = .028$) and although no statistically significant differences between the group characteristics, Grp2-6min were around 8 years younger (65 ± 12 years vs 73 ± 10 years; $p = .066$) which could account for their significantly faster walking pace. But although the mean baseline 6MWT distance and the mean walking pace (Grp1-2min 56.1 ± 16.1 m.min⁻¹ vs Grp2-6min 70.6 ± 13.6 ; $p = .042$) were significantly different between groups, participants performed at the same relative exercise intensities as noted by the similar HR, RPE, %HRR and HRWSI. The RPEs and %HRRs indicate that participants were walking at sub-

maximal intensities. Interestingly Grp2-6min walked 5% faster ($p = .007$) during the first 2 minutes of the baseline test compared to the practice test, possibly due to the effects of familiarisation, but as mentioned above, the pace had decreased significantly by minute 6 ($p = .040$). Another factor designed to alleviate such a reliability issue, which influences walking distance/performance as an outcome measure, is the use of a heart-rate- walking speed index.

The deviation around the mean at minute 2 in practice and baseline tests was $6.5 \text{ m}\cdot\text{min}^{-1}$ above or $7.0 \text{ m}\cdot\text{min}^{-1}$ below and $7.78 \text{ m}\cdot\text{min}^{-1}$ above or $11.14 \text{ m}\cdot\text{min}^{-1}$ below for baseline minute 2 vs minute 6 for Grp1-2min; $8.8 \text{ m}\cdot\text{min}^{-1}$ above or $15.5 \text{ m}\cdot\text{min}^{-1}$ below for Grp2-6min at 6 minutes. The mean difference for Grp1-2min at minute 2 and minute 2 vs 6 were small compared with the mean 2MWDs, and with a bias < 4 it therefore seems that the reliability of the 2MWT in terms of LoA was high.

3.6 Conclusion

It appears that both a two-minute and a six-minute practice test were equally effective in predicting baseline 6MWD in this cohort of patients with CHF. The significant correlations between 2MWT and 6MWT distance and pace concur with the findings of Leung et al. (2006) and suggest the good validity of the 2MWT, supporting the 2MWT as a practice test in this small cohort of patients with CHF. Comparison of HRWSI also appears to provide further evidence around reliability of a two-minute practice walk. These data have provided preliminary evidence that a two-minute practice test saves valuable clinical assessment time and is as effective in influencing pacing as a six-minute

practice walk for CHF patients being assessed by a 6MWT, whilst potentially reducing risk of fatigue seen in a 6MWT. A two-minute practice showed encouraging responses as a time-saving (and thus cost-saving) alternative. Ideally a third trial, either on the same day or on another day within one week would be required to assess whether a two-minute test does suitably achieve the same “reliability” needs as a six-minute test.

In summary, this study shows that a two-minute practice walk test achieves the same benefit as a full six-minute practice walk test prior to performing a baseline 6MWT, and that the use of HRWSI is considered an additional means of confirming the effects of familiarisation.

3b, Study 2

Reliability and oxygen cost validity of
a 4-inch step test in CHF patients

3.7 Abstract

Background: The assessment of functional capacity in patients with CHF has been performed by simple and easy to apply methods that are representative of everyday activities, such as the 6MWT. The starting MET values for the lowest step height (6-inch) of the current Chester step test (CST) protocol is 3.3 METs which, for many CHF patients is too high a starting point and does not allow them to perform the ideal 3 to 4 stages of the test to gain relevant data on function responses to exertion.

Objectives: to examine the reliability of a 4-inch (10 cm) step test protocol in beta-blocked patients with CHF.

Methods: 10 patients with CHF performed the CST twice on two separate days (CST1 and CST2), with at least five days between tests. CST1 was also performed to familiarise participants with the procedures of having to wear cardiorespiratory assessment equipment. HR, RPE and total number of steps were recorded in both tests and VO_2 was measured in CST2. A 3-minute duration was used at each stage due to the issues of slowed oxygen kinetics in CHF patients, as discussed by Walker et al. (2012) in their unpublished step test study.

Results: The characteristics of the CHF patients in this cohort were representative of those attending exercise-based CR programmes; mean age was 64 ± 15 years, 50% of patients had a history of IHD, mean LVEF was $< 30\%$, all were prescribed beta-blockade medication and half had atrial fibrillation. There were no intertrial differences between HR each minute of each of the stages 1 to 3 (stage 1 $p = .086$, stage 2 $p = .077$, stage 3 $p = .325$) and RPE (stage 1 $p = .287$, stage 2 $p = .165$, stage 3 $p = .289$). 95% LoA revealed acceptable agreement around mean HR. HR, RPE and VO_2 increased through the incremental stages of CST2; the end point of RPE 14 was achieved at a mean %HRR of $68.1 \pm 18.5\%$. Measured VO_2 was significantly lower than that predicted from the ACSM equation ($p = .005$).

Conclusion: In this small study on CHF, HR was reliable on a test re-test basis. VO_2 measures show the delayed oxygen kinetics and HR rise was blunted, all of which is in keeping with previous evidence of incremental exercise testing responses in CHF. The validity of estimated METs from an adapted CST for

CHF patients is questioned due to the discrepancy between estimates made using the ACSM (2008) calculation and the actual measures during CST2.

3.8 Introduction

3.8.1 Background

Assessment of cardiorespiratory fitness in CHF research studies is generally by the measurement of maximal oxygen uptake ($\text{VO}_2 \text{ max}$) or aerobic capacity. Factors considered to influence peak VO_2 include resting LVEF, chronotropic response, stroke volume response, skeletal muscle mass and vascular function, endothelial function and neurohormonal systems (Lainchbury and Richards, 2012). $\text{VO}_2 \text{ max}$ is usually defined as the point at which VO_2 reaches a plateau despite a further increase in work rate. In CHF such a plateau is rarely seen and thus is defined as peak VO_2 (Kemps et al., 2009). The VO_2 kinetics in response to increasing exercise intensity reflects delayed attainment of steady state in CHF patients (Zhang et al., 1993). Although maximal cardiorespiratory testing is the 'gold standard' method for establishing baseline fitness, exercise prescription and for assessing programme outcomes following an intervention, it is often impractical to use in CR settings due to costs of the equipment and the staffing time and expertise required (Sykes and Roberts, 2004). The use of valid outcomes from reliable and inexpensive tools to measure efficacy is vital for the National Health Service in the UK. The 6MWT is often used as an outcome measure for CHF-rehabilitation (Guazzi et al., 2009), however space may be lacking. The Chester step test (CST), designed by Sykes in 1995, can be used as a safe and practical outcome measure for CR programmes (ACPICR, 2009). It is a 5-stage incremental submaximal test, each stage lasting for 2 minutes. The test is externally paced by a metronome, with the stepping rate commencing at 15 steps per minute (spm) and progressing by 5 steps per minute per stage (Sykes, 2005). Measurements that can be recorded during

each minute of the CST include number of steps, HR, RPE and VO_2 . In the existing UK CR guidelines the recommended testing end points include a 75% percentage of maximum HR (%HR max) or 60% HRR and/or ≤ 14 RPE (Borg 6 – 20 scale; Borg, 1998) or Borg 4.5 CR-10. The current protocol is designed for using either a 6, 8, 10 or 12 inch step height, but the starting MET value at stage 1 using a 6-inch step is considered to be too great to allow for many lower functioning CHF patients to be able to complete the ideal of three to four stages required for estimating maximal exercise capacity. Having three or four stages also allows for establishing a relationship between HR and RPE and a corresponding work rate (METs) for physical activity guidance and exercise prescription (Latin et al., 2001; Sykes and Roberts, 2004; Buckley et al., 2004; ACSM Guidelines, 2008). However, the populations assessed to produce these estimates were younger and healthier than CHF populations attending CR exercise programmes. Improvement in CST performance can be quantified in terms of either an improvement in predicted peak metabolic equivalents (METs), duration to a predetermined HR or a lowered HR or RPE for any given work rate.

3.8.2 Reliability and validity of the CST

The literature review raises questions regarding the validity of sub-maximal tests for patients with CHF. Sykes and Roberts (2004) and Buckley et al. (2004) evaluated the use of the CST in healthy subjects. Sykes and Roberts (2004) assessed the test-retest repeatability of the CST in 68 healthy participants and found it to be good. The results demonstrated that the CST was a valid predictor of aerobic capacity in both males and females from a wide

range of ages (18 – 52 years) and fitness levels (Table 3.4), though its accuracy of prediction in subjects with an aerobic capacity of 25 – 68 ml/kg/min was poor (5 – 15%). Results from a relatively young and healthy cohort, however, are not likely transferable to a CHF population. The reliability and validity of the measures taken during the CST to predict VO_2 max and to prescribe aerobic exercise were evaluated by Buckley et al. (2004); including HR, RPE, age-estimated HR max and estimated VO_2 of each stage of the test (Table 3.4). The CST was performed twice, on different days, by 13 participants (7 males) aged 22 years. HR, RPE and actual VO_2 were the same at each stage for both trials. Intertrial bias \pm 95% limits of agreement (95% LoA) of HR reached acceptable limits at stage 4 of the CST, and for RPE at stages 3 and 4. Age predicted HR max significantly overestimated the actual HR max by 5 beats per minute ($\text{beat} \cdot \text{min}^{-1}$) ($p = 0.016$); in addition estimated versus actual VO_2 at each stage during both trials showed errors between 11% and 19%. Thus, in healthy participants the CST is a reliable test to detect improvements in aerobic fitness and a valid means to estimate metabolic equivalents, but its ability to predict actual VO_2 max is questionable.

There are no published studies to date assessing the use of the CST in patients with CHF, yet it is recommended for CR (ACPICR, 2009; BACPR, 2012). Two studies (Camargo et al., 2011; Karloh et al., 2013) have tested the reliability and/or validity of the CST in patients with Chronic Obstructive Pulmonary Disease (COPD). Camargo et al. (2011) examined the reliability of the CST in 32 patients with COPD and analysed the correlation with pulmonary function tests and exercise test results. Thirty two patients undertook 2 tests on different

days using a 20cm step; 31 patients completed stage 1 (2 minutes), 19 completed stage 2 (4 minutes), 7 completed stage 3 (6 minutes) and only 1 patient completed stage 4 and the first minute of stage 5 of the CST (9 minutes). The authors reported a significant correlation between the number of steps and 6MWD ($r = 0.60$, $p = 0.001$). Peak VO_2 was estimated from the CST in 6 patients only and was higher than that measured at peak of a cycle test (30.8 ± 5.1 ml/kg/min vs 17.4 ± 4.5 ml/kg/min, $p = 0.001$). The number of steps in the first and second test was highly reproducible (66 ± 41 steps vs 68 ± 41 steps) with no difference in HR between the 2 tests at peak exercise or at the end of each stage. This is in contrast to an early study by Swinburn et al (1985) who reported large inter-subject differences ($p < 0.01$) in step performance (range 14 – 126 steps) between the first and fourth attempts in 17 patients with severe chronic lung disease. It appears that the CST used by Camargo et al. (2011) was reproducible but was of a very short duration for the majority of patients with COPD. The authors therefore considered the CST an exercise testing protocol that was difficult for COPD patients to perform as most of their patients stopped during the second stage of the test. It would therefore seem that the same would be true for CHF. Karloh et al. (2013) used a 17cm step to investigate whether the CST was able to differentiate functional capacity and the magnitude of cardiorespiratory response of 10 patients with COPD (mean age 64 years) from 10 healthy subjects (mean age 63 years). The authors tested participants to 90% of HR max/or any limiting symptom and compared CST results with shuttle walk and 6MWT performances. The COPD group achieved 27% lower performance in the 6MWT, 42% lower in the shuttle walk and 49% lower in the CST, demonstrating that the CST was a valid tool in the

assessment of functional capacity of COPD patients and was able to distinguish them from healthy subjects. Unpublished data from a study by Walker et al. (2012) showed that VO_2 values at each stage of a CST using the standardised protocol were significantly lower in CHF patients than the ACSM estimates, and also demonstrated a slowed oxygen kinetics. METs estimates from a step test using two minutes at each stage therefore over-estimated exercise intensity for patients with CHF.

The prescriptive validity of the CST in relation to participants being treated with beta-blockade medication also remains unclear. Due to the blunting of the normal HR response to exercise by beta-blockers and chronotropic incompetence, VO_2 max predicted from the CST could easily be challenged at stages above 65% VO_2 max (Buckley et al., 2004). Beta-blockers reduce the attainable VO_2 max (Eston and Connolly, 1996) by causing a significant slowing of the kinetics of the oxygen transport system (Kowalchuk and Hughson, 1990). The ability to undertake physical activities is enabled by an increase in VO_2 in healthy adults this is achieved by a 2.2-fold increase in HR plus a 0.3-fold increase in stroke volume and a 1.5-fold increase in arterio-venous oxygen difference. Thus chronotropic incompetence can be a significant cause of/contributor to exercise intolerance and as such has a prominent role in CHF (Brubaker et al., 2011). Patients with CHF can have a reduction in peak VO_2 that is 15% to 40% below that of age-matched controls due to reduced cardiac output at peak exercise and abnormalities of skeletal muscle and vascular function (Sullivan and Hawthorne, 1995). As a result of impaired stroke volume,

patients with CHF must rely on increases in HR to augment cardiac output which is somewhat ironic as HR is often blunted (Brubaker and Kitzman, 2011).

The aim of this study was to examine the reliability of a commercially available step test but with a lowered step height to 4-inches (10 cm) in beta-blocked patients with CHF and to look at movement economy as an outcome. However, due to issues with equipment liability and patient recruitment the latter was not possible. The test was also adapted to using a 3-minute stage duration compared to the required 2-minute duration to make further assessments of the slowed oxygen kinetics in CHF patients, as discussed by Walker et al. (2012) in their unpublished study. The following hypothesis was explored: a modified CST is a reliable and suitable sub-maximal alternative test of functional capacity in patients with CHF.

Table 3.4 Reliability and validity of the Chester step test

Study	Participants	Diagnosis	Protocol	Key Findings
Sykes K and Roberts A. (2004)	68 subjects Mean age 30.6 ± 9.7 years (range 18 -52 years) 69% male	Healthy. Wide range of abilities.	VO ₂ max treadmill test. Completed CST on 2 occasions (CST1, CST2). 30 cm step. 15 spm initially, increasing by 5 spm every 2 minutes. End points 80% of maximum predicted HR or perceived exertion of 15 (Borg) or end of test (10 minutes).	High correlation between VO ₂ max and CST1 (r = 0.92, p < 0.001). Good test-retest repeatability; mean difference between repeated predicted measures -0.7 mlO ₂ /kg/min. LoA analysis showed that repeated measures were within 4.5 ml/O ₂ /kg/min, thus appropriate for use where a change in aerobic capacity is expected to be more than 3.8 mlO ₂ /kg/min higher than baseline. Limitation: transferability to CHF populations unclear. Conclusions: the CST was a valid test for the estimation of aerobic capacity in this group. The error of measurement was relatively small.

Study	Participants	Diagnosis	Protocol	Key Findings
Buckley JP, Sim J, Eston RG et al. (2004)	13 subjects Mean age 22.4 ± 4.6 years 54% male	Active subjects, participating in exercise or recreational sport 1 – 3 x per week.	Completed CST on 2 occasions (CST1, CST2), the second test 5 – 7 days after the first. A 30 cm step was used. 15 spm initially, increasing by 5 spm every 2 minutes. End points 90% of maximum predicted HR or perceived exertion of 17 (Borg) or end of test. On the third day, less than 7 days after CST2, a maximal treadmill test was performed.	<p>There was a linear RPE response. HR and VO_2 responses were curvilinear. RPE, HR and actual VO_2 were the same at each stage for CST1 and CST2. Measures between CST stages were significantly different ($p < 0.0005$). LoA of HR reached acceptable limits at stage 4 (-2 ± 10 bpm), and RPE at stages 3 (0.2 ± 1.4) and 4 (0.5 ± 1.9). Age-estimated HR max significantly overestimated actual HR max ($p = 0.016$).</p> <p>Limitation: transferability to CHF populations unclear.</p> <p>Conclusion: the reliability of the CST to detect improvements in aerobic fitness was recommended. Validity to predict VO_2, however, was questioned.</p>

Study	Participants	Diagnosis	Protocol	Key Findings
de Camargo AA, Justino T, de Andrade CHS et al. (2011)	32 patients with COPD Mean age 69.9 ± 9.0 years 91% male	COPD. FEV ₁ < 70% of predicted. Clinical stability (no change in medication dosage in the preceding 4 weeks).	<p>On 2 different days, at least 48 hours apart, patients were randomised to perform either two 6MWTs (30 minutes rest between the tests) or two CSTs (30 minutes rest period between the tests).</p> <p>A 20 cm step was used. Two minutes on each stage.</p> <p>The test was terminated by the patient (because of dyspnoea and/or leg fatigue) or by the physiotherapist if the patient was unable to maintain the cadence for 15 seconds.</p> <p>HR and SpO₂ were measured each minute. The main outcome of the CST was the total number of steps taken.</p>	<p>No differences between CST 1 and 2 in HR or SpO₂ at peak exercise or at the end of each stage, and the reliability analysis revealed high ICCs.</p> <p>The number of steps in the first vs the second CST showed a mean difference of -1.1 spm (LoA -20.2 to 17.9 steps).</p> <p>Significant correlation between number of steps and peak HR ($r = 0.55$, $p = 0.001$).</p> <p>Limitation: limited stages completed, which may have limited the accuracy of peak VO₂ estimates.</p> <p>Conclusion: The CST is highly reproducible in patients with COPD, but seems to be a difficult test for these patients.</p>

Study	Participants	Diagnosis	Protocol	Key Findings
Karloh M, Corrêa KS, Martins LQ et al. (2013)	<p>10 patients with COPD Mean age 64 ± 10 years 30% male</p> <p>10 healthy subjects Mean age 63 ± 7 years 30% male</p>	<p>COPD diagnosis based on clinical and spirometry criteria, minimum smoking history of 20 pack-years, clinical stability in the month prior to the beginning of the protocol and > 40 years of age.</p> <p>Sedentary individuals, with normal spirometry, no history of smoking and > 40 years of age were included in the control group.</p>	<p>Day 1: lung function evaluation and shuttle walk test. Day 2: the 6MWT. Day 3: the CST.</p> <p>A 17 cm step was used. Two minutes on each stage.</p> <p>End points: 90% of HR max/ when the subject could no longer keep the pace or displayed any limiting symptom.</p> <p>HR, blood oxygen saturation (SpO_2) and dyspnoea (modified Borg scale) measured before, immediately after and at the end of each level of the test.</p>	<p>The COPD group achieved a 48.8% lower performance in the CST.</p> <p>CST level achieved control vs COPD group 4.1 ± 1.1 vs 2.1 ± 0.9 ($p < 0.01$).</p> <p>Number of steps in the CST correlated with distance walked in the 6MWT ($r = 0.76$, $p = 0.02$).</p> <p>Limitation: tests were not performed in a randomised order.</p> <p>Conclusion: the CST is valid in assessing the functional capacity of patients with COPD and is able to differentiate them from healthy individuals. The HR response and dyspnoea induced by the test was similar in the COPD and control groups.</p>

3.9 Methods

3.9.1 Participants

A sub-group of 10 patients from the main intervention study were recruited to this study; all were referred to a hospital-based CR exercise training programme. The characteristics of the CHF participants in this cohort were representative of those attending exercise-based CR programmes in the UK (NACR, 2013); mean age was 64 ± 15 years, 50% had a history of IHD, mean LVEF was $< 30\%$. Participants were stable on optimal medical therapy for at least 4 weeks and had exertional dyspnoea, fatigue or both and were classified according to New York Heart Association functional class II to III. All were prescribed beta-blockade medication and half had atrial fibrillation. Women were well represented in this study (50%).

See Chapter 2 for details of recruitment, Hospital Trust and Regional Ethical approval, Patient Information and consent.

3.9.2 Procedures

Each participant performed the adapted CST twice on 2 separate days (CST1 and CST2), with at least 5 days between tests. CST1 was performed to familiarise participants with the procedures of wearing the cardiorespiratory assessment equipment where VO_2 was not measured, but the face mask was worn throughout the test. Testing was conducted using a metronome and a commercially-available 4 inch (10 cm) step. This step height was selected due to patients with CHF having a decreased exercise tolerance; a lower step allowing more of the test to be completed before reaching the end points.

Standardised instructions (detailed in Study 1) regarding RPE (Figure 2.1), Borg 6 – 20 scale (Borg, 1998), were given before each participant began stepping. Participants performed the CST using the techniques described in the CST manual (Sykes, 2005). Prior to the test commencing they were fitted with a pulse oximeter (Nonin Onyx II 9550 %SpO₂ digital fingertip pulse oximeter) to monitor HR. HR and RPE were recorded within the last 15 seconds of each minute of each testing stage. Maximum HR was estimated using the Keteyian Method and then used to calculate the test end point of 60% HRR. During CST2 the actual oxygen cost (VO₂; ml/kg/min) was measured continuously via an expired gas analysis system - Medgraphics Diagnostics Ultima™ Cardio²® CPX Training (MGC Diagnostics Corporation, St Paul, Minnesota). The system was calibrated before testing each participant using a 3 litre syringe for flow volumes across a range of flow rates and known gases for carbon dioxide and oxygen. The reported VO₂ was the average over the last 15 seconds of each minute at each stage of the CST. The estimated VO₂ for each stage of the CST was calculated using the ACSM (2008) Guidelines' equations.

3.9.3 Adapted Chester step test protocol

Resting blood pressure and HR were measured during pre-test screening using an automated sphygmomanometer on the left arm. Once connected to the Ultima™ (CST2 only) participants remained seated for 2 minutes before resting VO₂ and resting HR were recorded, followed by a further recording of both VO₂ and HR after standing for 2 minutes. The metronome was started at a stepping rate of 15 spm (stage 1) and participants were asked to commence stepping at the appropriate time and step rate for 3 minutes. If required, guidance was

provided to assist keeping the participant stepping 'in-time' with the required stepping rate set by the metronome. HR, RPE and actual VO_2 (CST2 only) were recorded during the last 15 seconds of each minute, while participants continued stepping. The CST continued to progress at an increase of 5 spm (i.e. stage 3, 25 spm; stage 4, 30 spm) until the participant reached an RPE of 14 and/or 60% HRR. The maximum test duration for the CST was 12 minutes (i.e. end of stage 4). Participants were able to change the lead leg, if they so wished, at the beginning of a new step rate. The total number of steps performed was recorded at the end of the test.

3.9.4 Data analysis

Data were assessed for the normality of their distributions via the Shapiro-Wilk prior to analysis. Assuming normality, data are expressed as mean \pm standard deviation (SD) with alpha set to .05. The one-way repeated measures ANOVA was used to examine differences between HR, RPE and VO_2 (CST2 only) each minute of each stage of the two tests.

The analysis then evaluated the difference in HR, RPE and VO_2

- a. Across 3 minutes of each stage and
- b. Between stages based on the value captured in the final 15 seconds of the stage

The Limits of Agreement (LoA) technique was used to assess the test-retest reliability for both HR and RPE between CST1 and CST2 as recommended by Buckley (2011). Pearsons correlation coefficient was used to examine

relationships between peak HR, peak RPE and total steps in both CST1 and CST2. Differences between predicted and actual VO_2 (METS) were found not to be normally distributed and thus the Wilcoxon signed ranks test was applied. All analyses were performed using SPSS version 21.

3.10 Results

Table 3.5 summarises baseline characteristics.

In both CST1 and CST2 all participants completed stage 1. Six participants completed stage 2 in CST1 and nine in CST2. Five participants completed stage 3 in both CST1 and CST2. One participant completed stage 4 in CST1 and two participants completed stage 4 in CST2.

Table 3.5 Patient baseline characteristics

Mean age (years)	64 ± 15
Male/female (n)	5/5
Body mass index (kg/m ²)	30.1 ± 5.1
CHF cause: idiopathic/ischaemic (n)	5/5
Left ventricular ejection fraction (%)	29 ± 7
NYHA class II/III (n)	9/1
Mean 6-minute walk distance (m)	438 ± 101
Prescribed beta-blockade medication (%)	100%

3.10.1 Reliability and reproducibility of the CST in CHF

Analyses have been performed on stages 1 to 3 as very few participants completed stage 4. There were no intertrial differences between HR and RPE

during stages 1 to 3 (HR: stage 1 $p = .089$, stage 2 $p = .077$, stage 3 $p = .325$; RPE: stage 1 $p = .287$, stage 2 $p = .165$, stage 3 $p = .289$). The HR at the end of the test was greater by 9 beat. min^{-1} in CST2 compared to CST1 (CST1 = 91 ± 17 , CST2 = 100 ± 16 beat. min^{-1} , $p = .0001$). RPE at the end of the tests were the same (CST 1 = 14.1 ± 0.3 , CST2 = 13.9 ± 0.9 , $p = .202$). There was no significant difference in the total number of steps between CST1 and CST2 (149.5 ± 81.8 vs 175 ± 69.8 , $p = .076$). The 95% LoA of HR and RPE are summarised in Tables 3.6 and 3.7 respectively. It was however only possible to evaluate responses during stage 1, as in stages 2, 3 and 4 there was only a small number of completed pairs of data.

Table 3.6 Limits of Agreement of HR (CST1 vs CST2) taken at minute 2 and 3 of stage 1 (bias $\pm 1.96 \times \text{SD}_{\text{diff}}$)

Stage of CST	Minute	95% LoA (HR- beat. min^{-1})
Stage 1	Minute 2	-1.0 ± 18.0
	Minute 3	1.6 ± 11.4

Table 3.7 Limits of Agreement of RPE (CST1 vs CST2) taken at minute 2 and 3 of stage 1 (bias $\pm 1.96 \times \text{SD}_{\text{diff}}$)

Stage of CST	Time	95% LoA (RPE)
Stage 1	2 min	-0.5 ± 3.0
	3 min	-0.5 ± 2.8

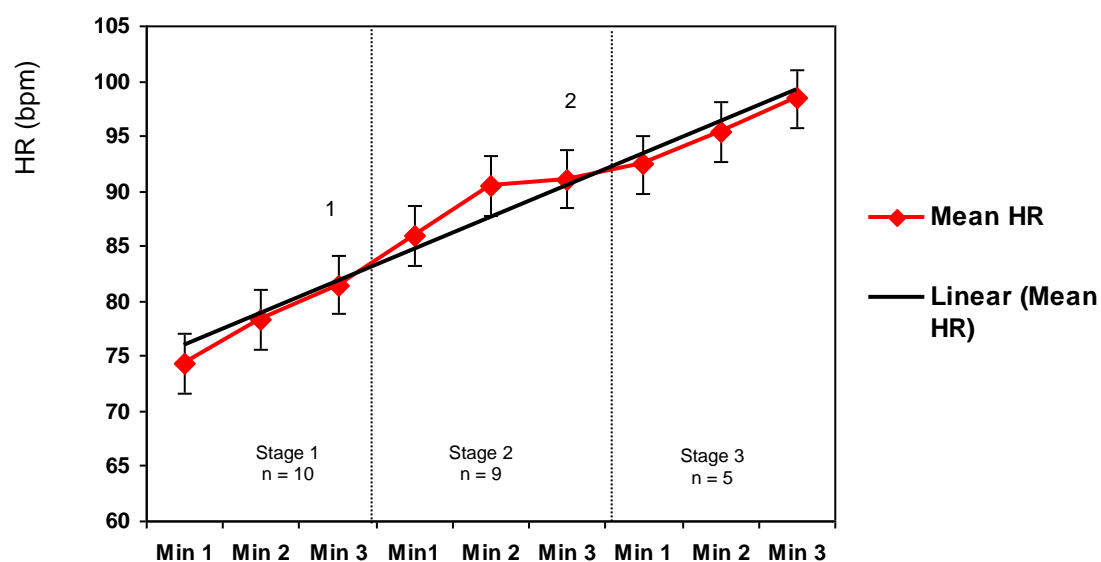
During stage 1 the 95% LoA ranged from 17 beat. min^{-1} above and 19 beat. min^{-1} below the small mean bias of -1 beat. min^{-1} . Examination of individual data

showed that the difference was 23 beats in one patient but in the remaining 9 patients it was ≤ 8 beats. RPE was as high as 2.5 scale points above or 3.5 below the mean bias in stage 1, but again this result was due to outliers. One patient had an RPE difference of 4 scale points but the remaining patients had either no difference, or a difference of 1 or 2 scale points. The small sample size of 10 participants does limit robustness of the LoA analysis.

3.10.2 HR, RPE and VO_2 responses during CST2

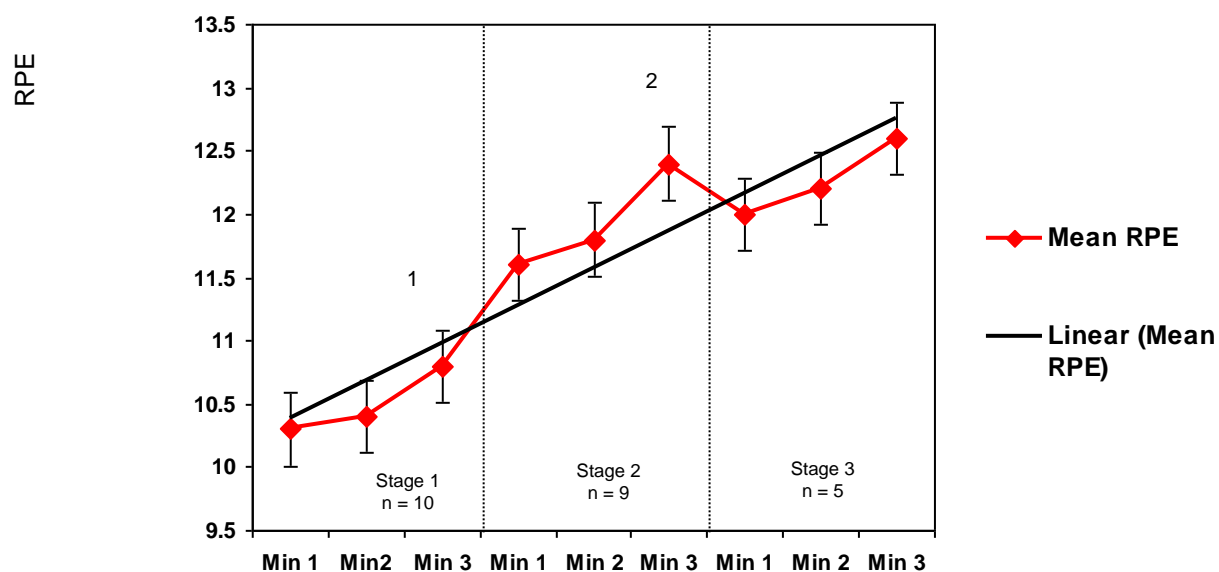
Six participants completed two CST stages (6 minutes), five completed three stages (9 minutes) and two completed all four stages (12 minutes). HR, RPE and VO_2 responses during each minute of each stage of CST2 can be seen in Figures 3.1, 3.2 and 3.3. Mean values show a gradual increase from the mean resting VO_2 of $2.8 \pm .7$ ml/kg/min as the intensity of exercise increased through the stages. Analysis using the one-way repeated measures ANOVA revealed significant differences with $p \leq .05$. The t-test for related samples found that HR and RPE had increased significantly from minute 1 to minute 3 during stages 1 and 2. The differences in HR between end stage 1/beginning stage 2, end stage 2/beginning stage 3 and between end stage 3/beginning stage 4 were not significant ($p = .109$; $p = .170$; $p = .106$ respectively). RPE however did increase significantly between the stages ($p = .004$; $p = .047$; $p = .058$ respectively). Increases in both HR and RPE were not statistically significant during stage 3, although the response remained linear (Figures 3.1 and 3.2). VO_2 however continued to increase significantly from stage 1 until the first minute of stage 4 (Figure 3.3). The differences in VO_2 between end stage 1/beginning stage 2 and between end stage 3/beginning stage 4 were also significant ($p = .001$; $p = .059$).

respectively). Change between end stage 2/beginning stage 3 was not significant ($p = .088$).



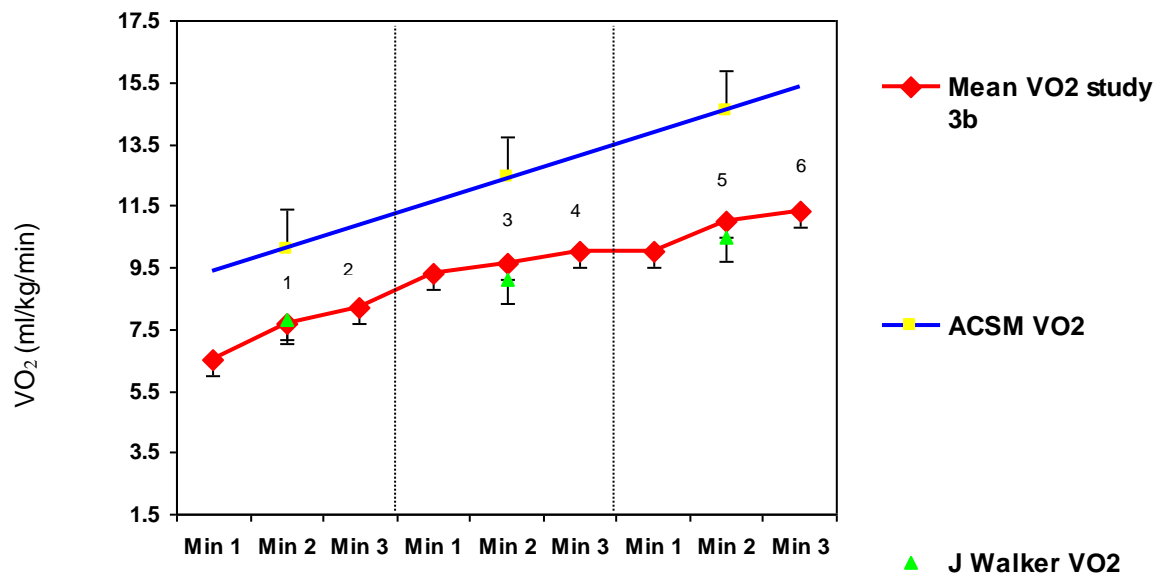
	Minute 1 HR(bpm) Mean(SD)	Minute 2 HR(bpm) Mean(SD)	Difference HR min 1 vs HR min 2 (p value)	Minute 3 HR(bpm) Mean(SD)	Difference HR min 1 vs HR min 3 (p value)
Stage 1	74 (8)	78 (11)	.105	82 (10)	.013 ¹
Stage 2	86 (34)	91 (7)	.23	91 (7)	.015 ²
Stage 3	92 (12)	95 (16)	.190	98 (13)	.069

Figure 3.1 Mean (SD) HR (beat. min⁻¹) at stages 1 to 3 of CST2



	Minute 1 Mean(SD)	Minute 2 Mean(SD)	Difference RPE min 1 vs RPE min 2 (p value)	Minute 3 Mean(SD)	Difference RPE min 1 vs RPE min 3 (p value)
Stage 1	10.3 (1.3)	10.4 (1.4)	.317	10.8 (1.5)	.015 ¹
Stage 2	11.6 (1.3)	11.8 (1.1)	.081	12.4 (1.4)	.021 ²
Stage 3	12.0 (1.0)	12.2 (0.8)	.157	12.6 (1.1)	.70

Figure 3.2 Mean (SD) RPE (Borg 6 – 20 Scale) at stages 1 to 3 of CST2



	Minute 1 Mean(SD)	Minute 2 Mean(SD)	Difference VO ₂ min 1 vs VO ₂ min 2 (p value)	Minute 3 Mean(SD)	Difference VO ₂ min 1 vs VO ₂ min 3 (p value)
Stage 1	6.5 (1.5)	7.7 (1.5)	.025 ¹	8.2 (1.5)*	.006 ²
Stage 2	9.3 (1.4)	9.6 (1.7)	.012 ³	10.1 (1.8)**	.005 ⁴
Stage 3	10.0 (2.0)	11.0 (1.9)	.013 ⁵	11.3 (2.2)	.013 ⁶

* Significant difference between VO₂ minute 2 and minute 3; $p = .001$

** Significant difference between VO₂ minute 2 and minute 3; $p = .003$

Figure 3.3 Comparison of mean (SD) VO₂ (ml/kg/min) at stages 1 to 3 of CST2 in Study 2 with ASCM (2008) predicted VO₂ and with the results from an unpublished study by Walker et al. (2012) using a three-inch step

There were significant modest to high correlations between end of test HR and end of test RPE ($r = 0.756$, $p = .011$), end of test HR and end of test measured (actual) VO_2 ($r = 0.771$, $p = .006$) and between end of test RPE and end of test measured (actual) VO_2 ($r = 0.659$, $p = .038$). The total number of steps during the test had significant high correlations with end of test HR ($r = 0.756$, $p = 0.011$), end of test measured (actual) VO_2 ($r = 0.717$, $p = .020$) and end of test RPE ($r = 0.727$, $p = .017$). End of test %HRR ranged from 40% to 95% of estimated HRR (mean %HRR $68.1 \pm 18.5\%$) and was significantly higher than end of test %HRR during CST1 (51.2 ± 20.2 ; $p = .0001$).

The measured VO_2 values were significantly lower than the predicted ACSM values ($p = .005$). In stages 1 and 2 actual values were 19% lower than the predicted values, in stage 3 they were 23% lower and in stage 4 they were 14% lower (Figure 3.5); in addition the actual values were similar to those seen in a study by Walker et al. (2012) using a 3-inch step (Figure 3.5). The estimated MET values at each stage were therefore also lower; final (estimated) METS were 22% lower ($p = .005$) than those predicted.

3.11 Discussion

3.11.1 Reliability and reproducibility

The CST manual (Sykes, 2005) does not recommend a practice test in order to familiarise participants with the test protocol. Initial comparison of HR and RPE at stages 1 to 3 of CST1 and CST2 would suggest that a practice test is unnecessary, which is similar to young, healthy subjects in keeping with

Buckley et al. (2004). In this current study end of test HR was statistically and clinically higher in CST2 (CST1 91.1 ± 17.5 beat. min^{-1} vs CST2 100.3 ± 16.7 beat. min^{-1} , $p = .0001$). HR reliability was good in nine of the participants; although the 95% LoA was 19 beats this seems to be a function of the low numbers. RPE was as high as 2.5 scale points above the mean in stage 1, which might not be acceptable in a clinical setting as it could be the difference between finding exercise moderate (13) and hard (15). But again, with only 10 participants, the individual variability may have affected the overall results and limited the robustness of the LoA analysis. In fact, during stage 1 of CST2, eight patients reported an RPE value that was the same or lower than that during CST1.

The similarity between CST1 and CST2 for RPE and total number of steps indicated that the CST is reproducible in CHF patients. Although the total number of steps was slightly higher in CST2 the difference was not statistically significant ($p = .076$) suggesting that the increase in total steps and final HR were due to familiarisation. Whether or not an increase of 25 steps (equivalent to an extra minute on stage 3) is clinically significant remains to be confirmed. Thus, for moderate intensity activity, the similar HR for the same stepping work rate, which led to participants exercising to a higher level on CST2, is a trend that appears to concur with previous studies on RPE in younger and older adults, including those with IHD (Lamb et al., 1999; Buckley et al., 2000; Buckley et al., 2004; Faulkner et al., 2007; Buckley et al., 2009; Buckley and Borg, 2011). However, there is little published on the reliability and validity of RPE in CHF.

3.11.2 HR, RPE and VO₂ responses during CST2

CST2 duration ranged from 5 minutes to 12 minutes, depending on the fitness of the individual. All participants completed 3 minutes (stage 1), six of the cohort completed 6 minutes (2 stages), five completed 9 minutes (3 stages) and two completed all 4 stages (12 minutes) using a low (4-inch step). In order to obtain valid data from an exercise test in CHF, small increments in workload and a total duration of 8 to 12 minutes are recommended (Lainchbury and Richards, 2012). Thus the total exercise time in the majority of patients was sufficient and useful for assessing cardiorespiratory responses (American Thoracic Society, 2003).

There is evidence of a blunted HR response during the CST, as there was no significant increase in HR from minute 1 to minute 2 in the first 3 stages of CST2 (Figure 3.3). This does not correspond to the VO₂ kinetics (Figure 3.5), which did show a levelling off; therefore HR in this cohort does correspond well to VO₂ as in healthy subjects, which is suggestive of chronotropic incompetence (discussed later). The end of test %HRR during CST1 (51.2 ± 20.2) was within the target %HRR range recommended by the ACPICR guidelines (2009) for patients with CHF (40 – 60% HRR) and slightly above the target range during CST2 (68.1 ± 18.5). Participants reached an end point of RPE 14 in CST2 which relates to a %HRR of approximately 70% therefore not dissimilar to the 68% HRR achieved. The high RPE values at a lower %HRR during CST1 (51%) could have been caused by participants overestimating RPE due to effects of beta-blockers (reduced HR response, reduced kinetics of the oxygen transport system and local muscle fatigue) and lack of familiarisation with the test. Alternatively, the test duration may have influenced the magnitude of

symptoms as much as the increments in work rate, which is in contrast to the findings of Kearon et al. (1991) who reported that the incremental changes during the CST determine the increase in perceived exertion. A shorter test may have improved reproducibility, but would not have been appropriate given the increases in VO_2 seen at each minute of the test.

The increases in HR were not statistically significant during stage 3, which could have been due to chronotropic incompetence. Chronotropic incompetence did not limit exercise capacity in a study of 16 patients with CHF (Clarke and Coats, 1995), and as increases in RPE paralleled HR in this current study it suggests that participants were not compromised by a blunted HR response. VO_2 continued to increase significantly until stage 4, which changes the linear relationship between HR, RPE and VO_2 . Nonetheless the significant moderate to high correlations between actual end of test VO_2 and end of test HR ($r = 0.771$, $p = .006$) and between end of test RPE ($r = 0.659$, $p = .038$) suggest that there remained a relationship between the values. HR and RPE appear to have reduced going into the latter stages, but this is likely to be a function of the number of participants reducing from 9 down to 5 and thus the data is based on remaining, fitter patients. The total number of steps during the test also had significant high correlations with final HR ($r = 0.756$, $p = .011$), actual final VO_2 ($r = 0.717$, $p = .020$) and final RPE ($r = 0.727$, $p = .017$).

Using the HR- VO_2 relationship to estimate peak VO_2 could be problematic in CHF due to the slowed oxygen kinetics (chronotropic incompetence), where the changes in the slopes of their respective responses to a given incremented step-height/work rate are not proportional as in healthy individuals (ACSM,

2008). There was a significant difference between the estimated (predicted) and the measured (actual) final VO_2 which intimates that abnormal HR responses during the CST can affect this estimate (predicted 14.8 ± 1.9 vs actual 11.7 ± 2.1 ml/kg/min, $p = .005$). Debigaré et al (2000) reported that a faster increment in work rate resulted in a lower HR observed during testing. Thus it seems that even 3 minutes at each stage may have been insufficient to allow appropriate HR responses in this cohort. Exercise prescription based on predicted peak VO_2 values and estimated peak METS would therefore be at a higher intensity than that using actual values attained and as such may be higher than patients with CHF might tolerate. Predicted (estimated) METS were 15 – 24% higher than the actual (estimated) METS at each stage; predicted (estimated) final METS being significantly higher than actual (estimated) end of test METS (4.2 ± 0.6 vs 3.3 ± 0.6 , $p = .005$). Interestingly mean VO_2 at rest was 0.7 ml/kg/min less than the value of 3.5 ml/kg/ O_2 on which METs estimates are based - 3.5 ml/kg/ O_2 being equal to 1 MET (Buckley et al., 2004). These differences are clinically significant for patients with CHF due to their poor exercise capacity; a difference of only 1 MET could result in some patients working at or above their ventilatory threshold.

3.12 Conclusions

The CST using a 4 inch (10 cm) step, and a duration of 3 minutes at each stage, appears to be a suitable submaximal exercise test for patients with CHF as all 10 participants completed the first stage (3 minutes) of the test, nine participants completed stage 2 (6 minutes) and five completed stage 3 (9

minutes). This test starts at a predicted workload < 3 METS, which appears to be acceptable to this cohort of patients with CHF. The CST was reproducible in this small cohort of CHF patients. Although no significant intertrial difference was observed in HR and RPE, the deviation around the means suggests that further trials with a larger cohort of beta-blocked CHF patients are required to confirm this finding.

In this study on patients with CHF, HR was reliable on a test re-test basis, but its validity is challenged as an indicator of oxygen uptake response and kinetics in comparison with healthy individuals where these two factors are normally closely linked. HR rise over the course of the 3-minute stages did not follow proportionate to the VO_2 . VO_2 continued to rise into the third minute, which shows the delayed oxygen kinetics, whereas HR rise was blunted (chronotropic incompetence), all of which is in keeping with previous evidence of incremental exercise testing responses in CHF.

In summary, an adapted, low CST is a reliable and suitable sub-maximal alternative test of functional capacity in patients with CHF, but the validity of estimated METs using the ACSM calculations from this test for CHF patients is questioned due to the discrepancy between estimates made and the actual measures during CST2. New MET estimation equations for CHF across a range of activities are likely to be required and warrant further investigation.

CHAPTER 4

Study 3:

Acute response of NT-proBNP following moderate intensity
exercise in patients with CHF

An abridged version of this chapter was presented at the American College of Sports Medicine Conference, May 2014 (Appendix 14)

4.1 Abstract

Background: Brain or B-type Natriuretic Peptide (BNP) is a marker of myocardial dysfunction and is reported to increase significantly following maximal exercise in patients with chronic heart failure (CHF). Little evidence, however, exists in relation to BNP response following recommended submaximal exercise sessions for patients with CHF. If raised levels of BNP do in fact affect physical function and health status, this knowledge may inform whether or not rest/recovery days are required between exercise sessions for patients with CHF.

Objective: This study aimed to assess changes to NT-pro BNP levels immediately, and at 24, 48 and 72 hours following a recommended CHF exercise training session.

Methods: 18 participants with CHF (14 males; aged 46 to 80 years), had venous blood samples taken at four time points following 20 to 30 mins continuous moderate intensity exercise (40 – 60% of heart rate reserve and/or Borg perceived exertion 12-13).

Results: Baseline (resting) and immediate post-exercise BNP levels were unchanged: 1741 ± 1991 ng/l and 1700 ± 1618 ng/l, respectively. These remained unchanged at 24, 48 and 72 hours post exercise: 1840 ± 2328 ng/l; 1550 ± 1710 ng/l; 1660 ± 1671 ng/l, although this cohort response does mask some of the individual variability as represented by the wide standard deviations.

Conclusion: Moderate intensity exercise training in most NYHA class II and III CHF patients does not acutely increase BNP levels and, therefore, there is no requirement for 'rest days' between exercise training sessions.

4.2 Introduction

The effect of exercise on plasma BNP levels in CHF patients has received little attention. As the half-life of BNP in plasma is 5 to 10 times longer than for ANP, which is cleared almost immediately, BNP may not be subject to rapid changes. The synthesis of BNP is considered to be regulated at a constant rate which would suggest that exercise of a short duration might not be sufficient to increase BNP secretion and thereby result in an increase in plasma levels (Kato et al., 2000). Results have been conflicting (see Chapter 1); with several studies reporting increases in plasma BNP levels immediately following exercise and others reporting that BNP levels do not increase with exercise. Krüger et al. (2004) interestingly reported a decrease in BNP levels following exercise in six of the 37 patients in their study. A similar finding was reported only in one previous abstract by Lainchbury et al. (2001).

The studies referred to have examined BNP responses only as far as 24 hours post acute exercise. This may not be a sufficient duration in pathological populations, especially moving beyond 24 hours post exercise where the longer term effects of acute exercise will be determined. CR standards and guidelines recommend that patients attend supervised exercise sessions at least twice per week, but there is no supporting evidence regarding the number of days there should be between sessions and knowledge of changes in BNP data would provide novel insight into the short and long term stress placed on the cardiovascular system by rehabilitation exercise and thus add to the debate about adequate recovery between sessions. In addition, it is not known whether baseline BNP levels contribute to the conflicting results published to date.

Further research may help establish clear recommendations regarding the frequency of exercise sessions for patients with heart failure (Leslie, 2010), thus the aim of this current study was to assess the changes in plasma NT-pro BNP immediately after, and at 24, 48 and 72 hours following a supervised CR exercise training session for patients with CHF.

The following hypothesis was explored: NT-proBNP does not increase following a moderate intensity exercise session.

4.3 Methods

4.3.1 Participants

The study population consisted of a subgroup of 18 patients in the main study (Study 4, Chapter 5). All participants had LVSD (determined via echocardiography) and were referred to a hospital-based CR exercise training programme. Participants were stable on optimal medical therapy for at least 4 weeks and had exertional dyspnoea, fatigue or both and were classified according to New York Heart Association functional class II to III. In contrast with several previous studies (Matsumo et al., 1995; Steele et al., 1997; Friedl et al., 1999 and McNairy et al., 2002), medication was not withheld prior to testing. See Chapter 2 for details of recruitment, Trust and Regional Ethics Committee approval, and patient information and consent.

4.3.2 Design and procedures

The measurements for this study were taken in the participants' third-week of their rehabilitation programme once they had been familiarised with the

structure and intensity of the standard exercise session (described in the next section). Blood was sampled using a polyethylene cannula placed in an antecubital vein in the left or right arm by a trained Research Nurse and collected into an EDTA (anticoagulant) sampling tube. Blood samples were collected immediately following and at 24, 48, and 72 hours after the exercise training session. Participants continued with their normal activities between these time points. The blood samples were transferred to the hospital's Clinical Chemistry laboratory as described in Chapter 2. Although BNP levels do not appear to rise and fall in any circadian rhythm (Jensen et al., 1997), samples were obtained at the same time of day to reduce the possibility of diurnal variation.

4.3.3 Training protocol

All patients were enrolled in an outpatient supervised exercise training programme where they attended twice per week for 12 weeks. The 12-week training programme is described in Chapter 2.

4.3.4 Data analysis

Data analysis was conducted using SPSS version 21.0 and alpha was set at the .05 level. Data were assessed for the normality of their distributions via the Shapiro-Wilk and for homogeneity of variance prior to analysis. It seems from previous research studies that baseline levels could possibly influence the kinetics of BNP/NT-proBNP thereby affecting the results; therefore patients were subdivided according to baseline levels. The related-samples Friedman's two-way analysis of variance by ranks test was conducted to measure

differences at each time point both for the cohort group and for the sub groups. The Mann Whitney U test was used to examine differences between sub groups. Spearman's rho was conducted to determine correlation coefficients. A partial correlation test was used to determine the correlation between NT-proBNP levels at each time point and also change in NT-proBNP levels between each time point, corrected for age.

4.4 Results

Table 4.1 summarises the patient baseline characteristics.

Mean resting HR increased from 64.3 ± 10.4 beat. min^{-1} to 88.8 ± 10.2 beat. min^{-1} during the exercise session, representing a mean of $45.0 \pm 19.8\%$ predicted HRR, and participants reported mean RPE values of 13.3 ± 0.8 . Mean NT-proBNP levels (Table 5.2) showed no significant change from baseline (pre-exercise) through all subsequent time points up to and including 72 hours post exercise ($p = .288$).

Table 4.1 Patient baseline characteristics

Mean age (years)	67 (12)
Male/female (number)	14/4
Body mass index (kg/m ²)	29.0 (4.1)
CHF cause: idiopathic/ischaemic (n)	5/13
Left ventricular ejection fraction (%)	32 (8)
NYHA class II/III (n)	13/5
Mean 6-minute walk distance (m)	416 (120)
Beta-blockade: bisoprolol/carvedilol (n)	16/2
ACE inhibitors/ARB-II (n)	12/5
Diuretics (n)	14

NYHA = New York Heart Association

ACE = angiotensin-converting enzyme ARB-II = angiotensin receptor blocker

Table 4.2 Mean NT-proBNP levels following exercise in 18 patients with stable CHF

	Baseline	Post exercise	24 hours post exercise	48 hours post exercise	72 hours post exercise
Mean NT-proBNP level (ng/l)	1741 (1991)	1700 (1618)	1840 (2328)	1550 (1710)	1660 (1671)

All values expressed as mean (standard deviation) Change in NT-proBNP levels at all time points NS (p = .288)

Significant modest correlations existed between age and NT-proBNP levels at rest and all time points during recovery (baseline $r = .56$, $p = .016$; post exercise $r = .56$, $p = .015$; 24 hours post exercise $r = .689$, $p = .002$; 48 hours post

exercise $r = .622$, $p = .006$; 72 hours post exercise $r = .621$, $p = .006$) (Figure 4.1). When corrected for age there remained a significant high correlation between NT-proBNP levels at all time points (baseline to post exercise $r = .958$, $p = .0001$; post exercise to 24 hours $r = .973$, $p = .0001$; 24 hours to 48 hours $r = .976$, $p = .0001$; 48 hours to 72 hours $r = .952$, $p = .0001$), confirming that there was no significant change in levels at each time point. Correlations between baseline NT-proBNP levels and BMI ($r = -.092$, $p = .717$) and LVEF ($r = -.099$, $p = .756$) were very low (NS), there was a low (NS) correlation between baseline NT-proBNP levels and NYHA class ($r = .203$, $p = .419$) and a modest correlation (NS) with 6MWD ($r = -.450$, $p = .061$).

There were modest to very high correlations, corrected for age, in the changes (Δ) in NT-proBNP levels between time points from baseline to 48 hours, with correlations becoming low (NS) at 48 to 72 hours (Δ baseline/post exercise and Δ post exercise/24 hours $r = -.607$, coefficient of determination 37%, $p = .010$; Δ post exercise/24 hours and 24/48 hours $r = -.913$, coefficient of determination 83%, $p = .0001$; Δ 24/48 hours and Δ 48/72 hours $r = .203$, coefficient of determination 4%, $p = .434$). Despite no significant “cohort” change consequent to exercise, the analysis of individual participant changes in NT-proBNP from baseline to 72 hours post exercise suggests a degree of heterogeneity (Figure 4.2) that are worthy of further examination.

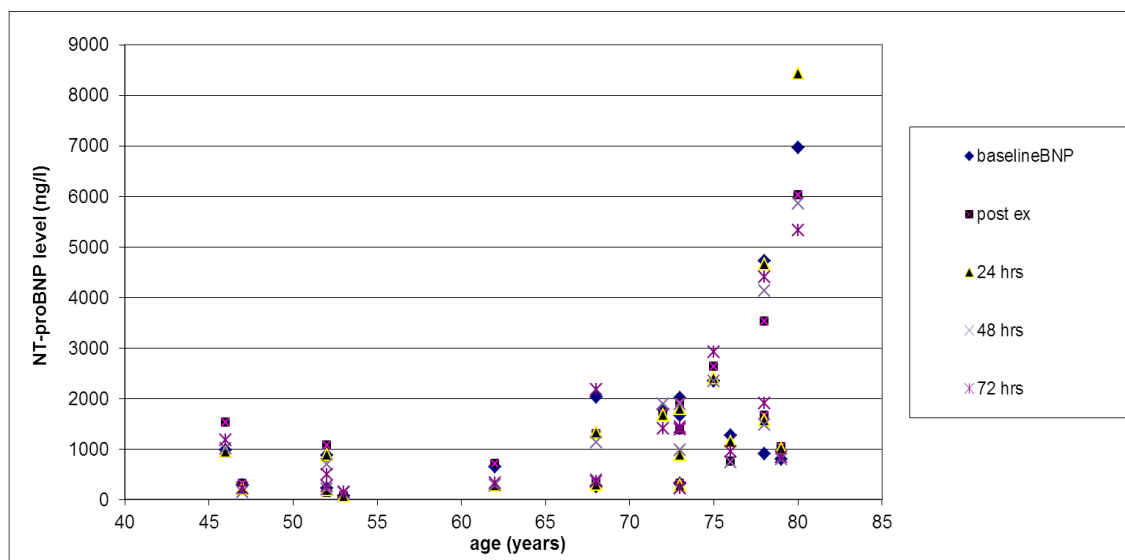


Figure 4.1 Acute NT-proBNP responses over 72 hours after exercise and its relationship to age in CHF patients

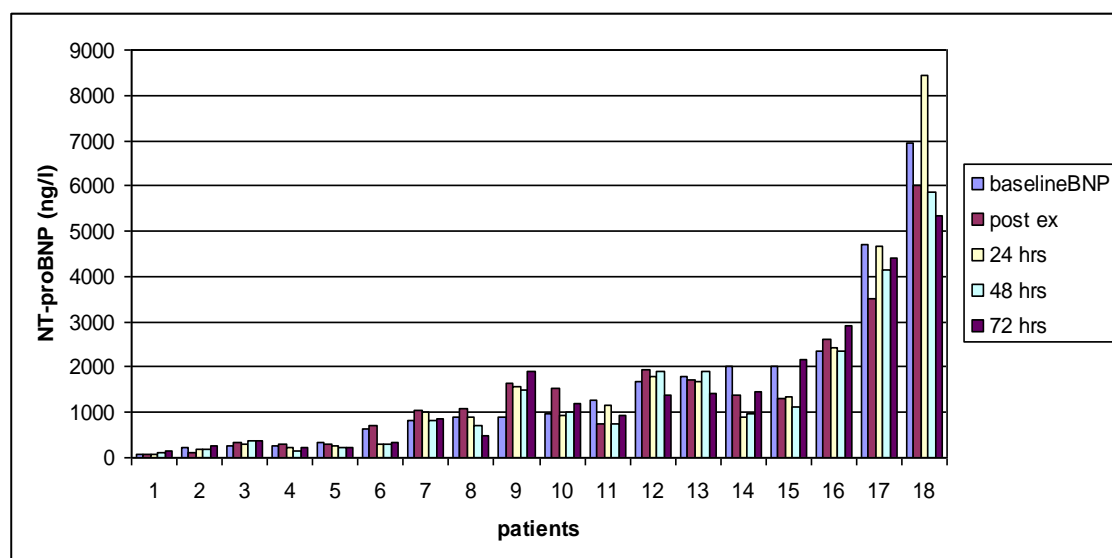


Figure 4.2 Kinetics of NT-proBNP immediately after and at 24, 48 and 72 hours post exercise, in rank order from the lowest participant's baseline level

Figure 4.3 highlights two subgroups, those who had an increase and those who had a decrease in NT-proBNP from baseline to immediately post-exercise.

Seven of the 10 participants who had resting NT-proBNP values < 1000 ng/l demonstrated post-exercise increases from a mean of 540 ± 341 ng/l at baseline to a mean of 715 ± 577 ng/l ($p = .051$). In contrast, 6 of the 8 participants who had baseline levels ≥ 1000 ng/l, demonstrated a decrease from a mean of 2848 ± 1967 ng/l at baseline to 2406 ± 1693 ng/l ($p = .069$).

Consequently, participants were divided into 2 subgroups for further data analysis; group 1 baseline NT-proBNP <1000 ng/l, group 2 baseline NT-proBNP ≥ 1000 ng/l (Table 4.3).

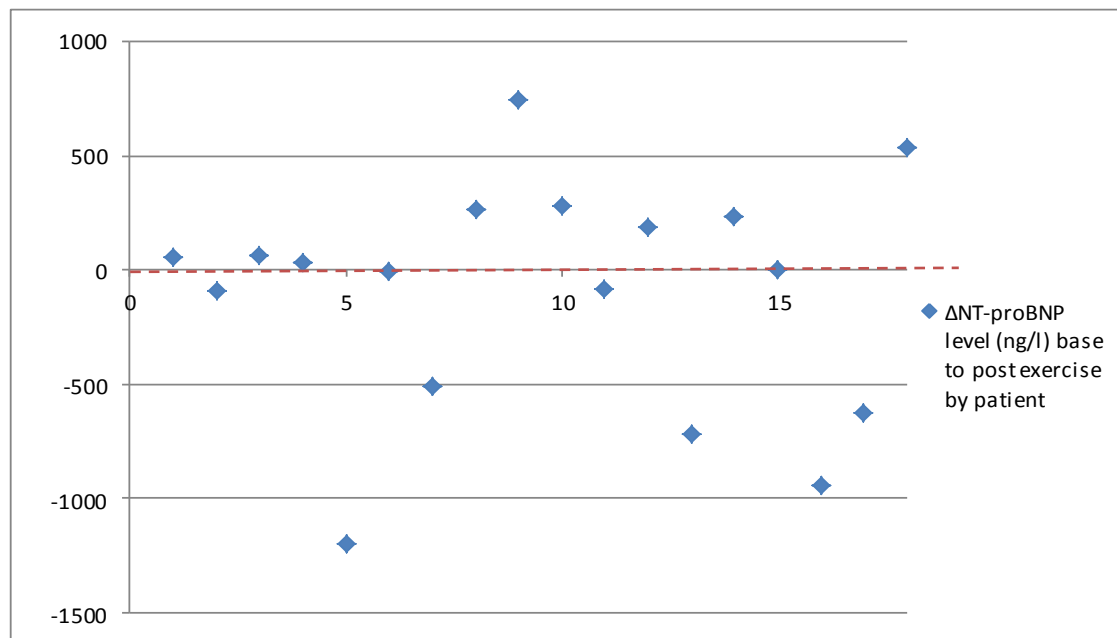


Figure 4.3 Baseline to immediate post exercise change in NT-proBNP level (ng/l) (x-axis is rank order of patients' resting NT-proBNP level; 0 – 10 had NT-proBNP values < 1000 ng/l and 11 – 18 >1000 ng/l)

Table 4.3 Change in NT-proBNP levels groups 1 and 2

Mean change	Group 1 baseline < 1000 ng/l	Group 2 baseline ≥ 1000 ng/l
Baseline to post exercise	175(26)*	-442(544)*
Post exercise to 24 hours	-137(204)	387(954)
24 hours to 48 hours	-41(103)	-419(910)
48 hours to 72 hours	60(157)	-13(599)

All values expressed as mean (± standard deviation)

**Δ significantly different between groups, $p = .043$*

Participants in group 2 were significantly older (Table 4.4): group 1 age 61 ± 14 years, group 2 age 75 ± 5 years; $p = .016$ and, by design, had significantly higher NT-proBNP levels at all time points (baseline: group 1 540 ± 341 ng/l, group 2 2848 ± 1967 ng/l, $p = .0001$; post exercise: group 1 715 ± 577 ng/l, group 2 2406 ± 1693 ng/l, $p = .003$; 24 hours: group 1 578 ± 494 ng/l, group 2 2793 ± 2568 ng/l, $p = .001$; 48 hours: group 1 537 ± 451 ng/l, group 2 2374 ± 1765 ng/l, $p = .001$; 72 hours group 1 597 ± 562 ng/l, group 2 2503 ± 1602 ng/l, $p = .001$). There was a significant difference between groups (Table 4.3) in the change in NT-proBNP levels between baseline and immediately post exercise (group 1: $+175 \pm 267$ ng/l, group 2: -442 ± 544 ng/l; $p = 0.043$). The

mean NT-proBNP levels showed no significant change within the groups from baseline through all subsequent time points up to and including 72 hours post exercise (group 1 $p = .183$; group 2 $p = .434$).

Table 4.4 Characteristics of sub groups 1 and 2

	Group 1 (n=10) < 1000 ng/l	Group 2 (n=8) >1000 ng/l	p value
BMI (kg/m ²)	28.7(3.8)	29.5(4.9)	.705
LVEF %	33(8)	32(9)	.970
6MWD (m)	457(119)	351(99)	.138
Age (years)	61(14)	75(5)	.016
Male/female	9/1	5/3	
Number of sessions pre testing	6(4)	9(9)	.192

Values expressed as mean (\pm standard deviation) Group 1 baseline NT-proBNP <1000ng/l, group 2 \geq 1000ng/l

4.5 Discussion

In a small cohort of NYHA II and III CHF patients performing a moderate intensity exercise programme (%HRR = 45.0 ± 19.8 ; RPE 13.3 ± 0.8) there was no significant change in NT-proBNP levels. The very low (NS) correlations between baseline NT-proBNP levels and a number of health markers rule these markers out as influencing factors on raised NT-proBNP; BMI ($r = -.092$, $p = .717$); LVEF ($r = -.099$, $p = .756$); NYHA class ($r = .203$, $p = .419$); 6MWD ($r = -.450$, $p = .061$). There are conflicting results in the current evidence on the link between exercise and raised plasma BNP. Several studies have reported non-significant changes in plasma BNP levels following exercise in patients with

CHF (Friedl et al., 1999; McNairy et al., 2002; Krüger et al., 2004; Normandin et al., 2013). The most likely reason for the observed results in this current study is that the exercise was not at an intensity sufficient to cause substantive increases in preload and thus myocyte stretch that would lead to circulating NT-proBNP levels to increase. Only 44% of the cohort was exercising at or above 45%HRR. There are, however, other possible reasons or contributing factors that warrant further investigation. Unchanged BNP levels following exercise could be a result of increased BNP clearance, due to enhanced enzymatic degradation of BNP by neutral endopeptidase (NEP) (Krüger et al., 2004). NEP is widely expressed, with the highest concentrations being present in the renal proximal tubules (Mangiafico et al., 2013); therefore assessment of differences in renal function in future studies may help explain this.

Another pathophysiological mechanism that could be responsible for the results of this study includes a reduction in BNP production and/or release during exercise (Krüger et al., 2004). In symptomatic CHF, the already compromised ventricles may fail to synthesize BNP relative to the demands of the system. This would lead to impaired capacity to release and regulate active BNP in response to exercise-associated acute volume expansion with corresponding increases in ventricular pressure thereby limiting the ability to maintain homeostasis in response to the demands placed upon the myocardium. This may explain the differences observed in the sub-analysis between groups of differentiated baseline NT-proBNP levels, whereby 60% of patients in group 1 (baseline NT-proBNP level < 1000 ng/l) had a seemingly appropriate small yet $\geq 10\%$ increase in NT-proBNP level immediately post exercise compared with

only 25% in group 2 (baseline NT-proBNP level ≥ 1000 ng/l). In contrast 63% of patients in group 2, i.e. those with NT-proBNP levels indicating more severe CHF, had a $\geq 10\%$ decrease in NT-proBNP level immediately post exercise, compared with only 10% in group 1. When comparing the mean values at baseline and post exercise, in group 1 there was a 24% increase - not of statistical significance but possibly of clinical significance (Koglin et al., 2001) - and in group 2 a 16% decrease (NS) in NT-proBNP level. In group 1 the mean value returned to within 7% of baseline at 24 hours post exercise and was lower (NS) than baseline 48 hours post exercise. Although the changes from baseline to post exercise were not significant, they demonstrate a trend in both groups that could be explored in further, larger studies. These findings are in accord with the results of the study by Krüger et al. (2004), as 16% of patients in their study also had an observed reduction (NS) in BNP levels following exercise (mean age 71 years compared with 57 years in the group with an observed increase). Lainchbury et al. (2001) previously reported a similar finding in their abstract; although the overall mean BNP increased with exercise in 68 patients with NYHA class III to IV CHF ($p < 0.05$), BNP decreased immediately following exercise in a group of 15 CHF patients (-1.5 ± 2.8 pmol/l), seven (45%) of whom died in follow-up. Those who died had a higher incidence of IHD, lower LVEF and higher baseline BNP (52 ± 20 vs 33 ± 24 pmol/l, $p = 0.013$). Only eight of the 53 (15%) patients who had an increase in BNP during exercise died during the two-year follow-up period. In the study by McNairy et al. (2002), although patients with a higher baseline BNP level (1712 ± 356 pg/ml) had an increase in BNP (NS) following exercise; it was less of an increase (18%) than those with a lower (126 ± 26 pg/ml) baseline level (30%).

As previously discussed in Chapter 1, Mangiafico et al. (2013) stated that there is a growing body of evidence suggesting that dysregulation of the natriuretic peptide system exists in cardiovascular disease and HF. The authors report that increased BNP levels seen in patients with CHF were initially thought to be due to the body's attempt to compensate for the increased water retention and cardiac stress associated with LVD. Recent studies using more sensitive technologies demonstrate that, in patients with CHF and high plasma BNP levels assessed by conventional assays, that there is a lack of mature BNP. Thus, despite the elevated levels of BNP seen in advanced CHF, sensitive mass-spectrometry indicates that less biologically active precursors and multiple degraded forms of BNP are actually present. This suggests that altered processing of BNP occurs, resulting in a deficiency of the hormone and thereby its protective properties. This factor could also have contributed to the results of this study in that the compromised myocardium may have failed to release active BNP in response to exercise, particularly in group 2 with baseline NT-proBNP levels ≥ 1000 ng/l.

4.6 Limitations

There are some limitations of this study and specifically the effect of medications on BNP. In this study, 89% of patients were prescribed bisoprolol, a non-vasodilating beta-blocker, 67% an ACE inhibitor and 78% diuretic medication. Diuretics and ACE inhibitors can reduce BNP levels, and some beta-blockers can increase them in the short term (Cowie et al., 2010). Even so, medication is unlikely to have had an impact on NT-proBNP levels in this study

as all patients were optimised on CHF medication and were stable for at least 4 weeks prior to recruitment. Second, the mean number of exercise sessions attended prior to undertaking this study was 7, therefore it is possible (albeit unlikely) that there had been a minor training effect not seen in previous studies of CHF populations. Scharhag et al. (2008) proposed that myocardial response or adaptation both during and following exercise might be regulated by the release of BNP as a study in healthy athletes showed higher increases in NT-proBNP levels in nonelite runners with lower training distances. This suggests that training reduces BNP production during exercise. Increased release of BNP seen in other studies could therefore be due to acute myocardial stress initially when commencing exercise (Scharhag et al., 2008) in severely deconditioned and non-active patients. Finally, although a relatively small study population of 18, the sample size is comparable with other published studies investigating the kinetics of BNP in response to exercise.

4.7 Conclusion

The results of this current study, undertaken in routine clinical practice with a representative population of UK CHF patients, confirm that moderate intensity exercise training does not acutely increase NT-proBNP levels in NYHA class II and III patients. It appears that patients with already high NT-proBNP levels do not have an increase in NT-proBNP immediately following moderate intensity exercise or in a subsequent 72-hour period. The results do, however, reveal individual variability in the acute response of NT-proBNP release to exercise that is worthy of further study. At this point in time there are no NT-proBNP data that point to a requirement for 'rest days' between exercise training

sessions. The dose and the mode of exercise that will elicit a physiological increase in NT-proBNP are yet to be confirmed. The hypothesis - NT-proBNP does not increase following a moderate intensity exercise session – is accepted.

CHAPTER 5

Study 4

The efficacy of exercise-based cardiac rehabilitation for class II and III heart failure patients

5.1 Abstract

Objective: This study investigated the efficacy of a moderate intensity exercise rehabilitation programme for participants with heart failure (CHF). Outcomes included changes in functional exercise capacity, cardiac biomarkers cardiac function and quality of life (QoL).

Methods: 51 patients (37 male) aged 30 to 84 years were recruited as participants into the study. Participants were randomised into either the early intervention group (EI, n = 30) or a delayed intervention “control” group (DI, n = 21). All participants underwent an initial assessment (T1) at baseline including a six-minute walk test (6MWT), NT-proBNP levels, cardiac function (echocardiography), NYHA class and QoL questionnaire scores. The (EI) group performed a 12-week course of supervised exercise training followed by a second assessment (T2). During this period the DI group continued to follow routine advice and were similarly reassessed at 12 weeks before starting their exercise programme. All participants were assessed at 36 – 48 weeks (T3).

Results: There were no adverse events during or as a result of the exercise sessions or during the exercise testing. For a target rating of perceived exertion, the 6MWT distance increased from 398 ± 100 m to 423 ± 108 m ($p < .0001$). The corresponding heart-rate-walking speed indexes at these two time points were 16.3 ± 7.3 and 15.3 ± 8.7 ($p < .0001$). Pre- and post-programme NT-proBNP levels were 1174 ± 1495 ng/l and 1094 ± 1307 ng/l, respectively ($p = .381$) There were no changes in cardiac function. NYHA scores improved from $2.3 \pm .5$ to $1.8 \pm .6$ ($p < .0001$) in the EI group and QoL scores were unchanged.

Conclusion: In following a programme of exercise based on national guidelines and systematic reviews, exercise training in a group of CHF participants was found not to be detrimental. It enhanced functional exercise capacity with a

corresponding improvement in NYHA class. However, unlike some previous studies NT-proBNP was unchanged. It is possible that such changes could be linked to exercise intensity and that a moderate intensity programme performed twice per week was not enough of a stimulus to invoke a change in NT-proBNP levels. Further research is required to evaluate the dose of exercise training linked to beneficial changes in NT-proBNP levels but in spite of this, moderate intensity exercise continues to show a consistent benefit to functional capacity and QoL.

5.2 Background

Wolverhampton's CR Service has long-established exercise training programmes for patients following myocardial infarction, coronary revascularisation (coronary artery bypass graft or angioplasty) and cardiac valve surgery. Until July 2005, however, there was no such provision for patients with CHF. The National Service Framework for Coronary Heart Disease (DOH, 2000) suggested that early access to CR should be considered as an option for patients with CHF thus funding was secured for a 3 year period to provide a 12-week course of exercise training for patients diagnosed with CHF. Additional non-recurring funding was secured for NT-proBNP testing for the purpose of evaluating the efficacy of the exercise programme and the outcome measures were published in the form of a service audit (Leslie and Buckley, 2010). Results demonstrated that a structured exercise training programme favourably influenced functional capacity and NYHA class, with encouraging trends related to NT-proBNP levels. Natriuretic peptide testing is invasive and is therefore not recommended as an outcome measure to be used routinely by CR departments; however it may provide additional evidence for the efficacy of exercise training for patients with CHF to add to the limited body

of evidence that currently exists. The ExTraMATCH Collaborative (Piepoli et al, 2004) recommended that further research should focus on optimising exercise programmes and identifying appropriate patient groups to target. Following the service audit the proposal for this local study received ethical approval.

5.3 Introduction

Poor performance on the 6MWT has been related to severity (Guyatt et al., 1985) and prognosis (Bettencourt et al., 2000) in patients with CHF. Aerobic exercise is recognised by current CR guidelines as a safe and well-established means of improving the pathophysiological and clinical symptoms of CHF to supplement pharmacotherapy. Indeed, individual randomised controlled clinical trials and meta-analyses have demonstrated that exercise training is safe, improves functional capacity, QoL and NYHA class in patients with CHF. Furthermore, neurohormonal factors such as BNP or NT-proBNP also appear to be useful markers of severity in patients with CHF and thus a reduction in these levels would suggest an improved prognosis. Several studies (see Chapter 1) have demonstrated that exercise training reduces NT-proBNP levels in CHF. Prescription of appropriate and adequate training intensities is crucial to obtaining exercise-induced benefits whilst at the same time guaranteeing patient safety. Continuous and interval training are two methods of aerobic exercise that have been proposed for CHF patients. Continuous aerobic training is typically performed at moderate intensity in steady-state conditions. In contrast interval training – not currently recommended in published UK guidelines - comprises of high intensity exercise in repeated short bouts (usually up to 2 minutes duration) with active recovery periods between (Carvalho and

Mezzani, 2011). The majority of the published studies have exercised patients at a percentage of VO_2 peak (often between 50% and 70%, but occasionally up to 95%) using continuous aerobic exercise training on cycle ergometers and treadmills.

5.3.1 Aerobic exercise training prescription

The lower limit of aerobic exercise intensity that can be prescribed in order to ensure exercise-induced benefits remains unconfirmed, but intensities as low as 40% peak VO_2 have been proven to be effective in CHF patients (Belardinelli et al., 1995). CR providers follow the guidelines recommended by the BACPR (2012) and the ACPICR (2009). The ACPICR suggest a target HR of 40 – 60% of HRR and/or RPE of 12-13 on Borg's scale. HR is routinely used for exercise prescription due to the existing linear relationship between HR and VO_2 and Borg scale RPE values between 11 and 13 are reliable for exercise training prescription in CHF patients on beta-blockers, assuring an energy expenditure lying between the first and second ventilatory thresholds (Carvalho et al., 2009). The professional standards and guidelines advocate the use of sub-maximal tests to prescribe exercise, with the suggested HR training targets and training intensities being somewhat lower than those used in the published trials. CHF research studies have invariably used maximal exercise tolerance testing to measure peak VO_2 , a percentage of which is then used to set training targets; however, this is not the case with existing routine clinical practice as few CR centres have the necessary facilities for maximal testing. Walking tests are often used to assess patients with CHF and to provide an outcome measure in

CR, but walk distance alone can be a misleading outcome due to other influencing factors (Buckley et al., 2010).

5.3.2 Six-minute walk test performance and heart-rate-walking speed index

Increased 6MWD is routinely used as an outcome measure for CHF-rehabilitation (Guazzi et al., 2009) and correlates with activities of daily living and quality of life (Enright, 2003). In order to be considered as related to the intervention, the improvement in distance walked must be at least > 5% from baseline (Rostagno and Gensini, 2008); however, if the increase in distance is less than 10%, even with statistically significant results, the variation is quite possibly due to familiarisation (Opasich et al., 1998). Improvements in 6MWT performance ranging from 30 m (Guyatt et al., 1985) to 90 m (Spertus et al., 2005) have all been associated with a significant improvement in walk performance. Shoemaker et al. (2012) used a novel approach for triangulating the Δ 6MWD that should be regarded as clinically meaningful and concluded that a Δ 6MWD of approximately 45 m exceeded measurement error and was associated with significant changes in either aerobic capacity and/or QoL. The HRWSI was first proposed by Buckley et al. (2010) as a method of determining the contribution of physiological changes to improved walking performance following CR, thus providing a more accurate reflection of improvements in aerobic fitness regardless of how much or how little walking performance improved.

5.3.3 Natriuretic peptides

The levels of natriuretic peptides denote the severity of CHF and also reflect the body's attempt to compensate and maintain homeostasis (Koglin et al., 2001) in cardiac function. Interventions to reduce levels of BNP/NT-proBNP are clearly of importance in the management of CHF, and evidence demonstrates that pharmacotherapy can reduce BNP as a result of the favourable effects on cardiac remodelling (McCullogh, 2004). Seven of nine selected individual studies included in a meta-analysis by Smart and Steele (2010) demonstrated that moderate intensity exercise training, with a minimum weekly energy expenditure of 400 to 450 Kcal, reduced BNP and NT-proBNP independent of frequency and duration of training. This was conceivably due to a blunted neurohormonal response at rest and a consequent reduction in BNP release (Passino et al., 2006).

5.3.4 Left ventricle function

Left ventricle remodelling is a significant process in the progression of HF and involves several factors, including neurohormonal and haemodynamic derangement. There is progressive chamber enlargement and deterioration in "pump" function as a result of increased haemodynamic load and neurohormonal stress (Haykowsky et al., 2007). End-diastolic volume (EDV) and end-systolic volume (ESV) increase; there is wall thinning and a change in left ventricle shape, usually accompanied by a reduction in LVEF. Several studies investigating the effect of exercise training on BNP and NT-proBNP levels have found a reduction in post training natriuretic peptide levels and a

corresponding increase in LVEF (Passino et al., 2006; Passino et al., 2008; Rengo et al., 2014), a reduction in end-diastolic volume (EDV) (Conraads et al., 2004; Passino et al., 2006) and an increase in diastolic filling (Conraads et al., 2004; Giallauria et al., 2006).

5.3.5 Pulse pressure

Low PP has been reported to be an independent predictor of mortality in patients with decompensated heart failure (Aronson and Burger, 2004), in patients with advanced CHF (Voors et al., 2005; Petrie et al., 2009; Yildiran et al., 2010) and in patients with symptomatic left ventricular dysfunction post myocardial infarction (Petrie et al., 2007). The effect of PP on exercise training outcomes for patients with CHF has previously been reported in a retrospective study (Leslie and Buckley, 2012). However, this warrants further investigation under research conditions.

5.3.6 Quality of life

Pooled data from nine studies in a review by van Tol et al. (2006) showed a significant decrease of almost 10 points in the MLHFQ score, which is considered clinically meaningful (Piña et al., 2003). As with previous reviews, there were no trials reported to have used the HADS. However, a meta-analysis by Rutledge et al. (2006) did include one study that used the HADS to measure depression in an intervention study in patients with CHF, which showed no significant improvement (49 ± 7 vs 48 ± 8 , $p = 0.39$). The recently published update of the Cochrane Review (Taylor et al., 2014) included 33 trials, 19 of

which reported the use of a validated QoL measure; 13 used the MLHFQ and 2 used the HADS (see Chapter 1).

5.4 Objectives

The primary objective of this study was to assess the physiological and psychological effects of moderate intensity exercise training on patients with CHF and to provide new evidence examining the correlation between functional capacity, NT-proBNP levels and QoL following a 12-week course of supervised exercise.

The following hypotheses were explored:

In a representative sample of a UK CHF population, compared to that reported in the current evidence, a 12-week exercise programme applying current UK guidelines, will result in:

- (i) An improved functional capacity
- (ii) A reduction in plasma BNP levels and an associated improvement in LV function
- (iii) An improvement in QoL
- (iv) Demonstrating a strong correlation between changes in functional capacity, with changes in plasma BNP levels and in QoL.

5.5 Methods

5.5.1 Participants

Hospital records of 92 patients referred to the hospital-based CR exercise programme were screened to assess suitability for recruitment to the study. All patients had LVSD (detailed previously). Patients were stable on optimal medical therapy for at least 4 weeks and had exertional dyspnoea, fatigue or

both and thus were classified according to NYHA functional class II to III. Of the 76 that were suitable, four patients decided that they no longer wished to start the exercise programme, three failed to attend, four chose not to join the study and three did not fulfil the inclusion criteria when they attended for initial screening assessment. A total of 62 patients were recruited and gave their written consent to join the study; 38 randomised into the early intervention (EI) group and 24 to the delayed intervention (DI) group. See Chapter 2 for details of recruitment, approval from the Royal Wolverhampton NHS Trust's Research and Development Committee and from the Regional Ethics Committee, and for patient information and consent.

5.5.2 Design and procedures

General methods and protocols are described in Chapters 2 and 3. Medication was not withheld prior to testing. The initial pre-screen was performed during T1 as described in Chapter 2; all patients performed either a two-minute or a six-minute practice walk test. All tests and measurements were repeated at T2 and T3.

Measurements

Functional Exercise Capacity Test: Patients were assessed using the 6MWT of functional capacity (Butland et al, 1982). Resting and recovery HR and blood pressure were recorded pre and post testing. HR, RPE and distance walked were recorded at each one-minute interval during the test. The 6MWT was stopped if HR exceeded 60% of HRR, if the patient reported an RPE > 13 or reported symptoms of discomfort such as increased shortness of breath, chest

pain or dizziness. All patients were familiarised with the 6MWT at T1. A two-minute practice walk was employed following validation in Study 1 (Chapter 3a). HRWSI was calculated by dividing total heart beats during the 6MWT by the 6MWT distance and multiplied by 10 to describe heart beats per 10 m walked (see Chapter 2 for further details). Due to the constraints of the study and limited resources, it was not possible to perform a planned subgroup CPEX analysis using the modified CST (as described in Study 2, Chapter 3b) to compare with the results from the 6MWT.

Plasma BNP Levels: A venous blood sample was obtained prior to the 6MWT at T1 and T2 to determine the plasma levels of NT-proBNP. Samples were immediately sent to the Clinical Chemistry laboratory to be centrifuged and serum stored at -20 °C prior to analysis with a chemiluminescence sandwich immunoassay (see Chapter 2 for further details).

Left Ventricle function - Echocardiography: A subgroup (n=20) was randomly selected from both groups to undergo echocardiography at T1 and T2 to determine whether there was a significant change in left ventricular function and to evaluate cardiac function using tissue doppler imaging. For the protocol see Appendix 15. Two-dimensional resting echocardiographic recordings were obtained in both the initial and the second assessment, with participants lying in the left lateral supine position, using a Philips Epiq (Philips Healthcare) Ultrasound system. All measurements (Appendix 15) were obtained by experienced British Society of Echocardiography accredited cardiac physiologists blinded to group assignment and intervention. Images were saved

on the Xcelera system and compact disc using the participant's individual identification number. The variables considered were LVEF (using the biplane Simpsons method), LV end-systolic and end-diastolic volumes, LV wall thickness and internal dimension.

- *Pulse pressure*: The retrospective study by Leslie and Buckley (2012) provided a basis for the PP investigations in this study (Appendix 16). Recordings of SBP and DBP were taken before and immediately after the 6MWT, in the supported right or left arm of the seated patient with a cuff-size adjustment based on arm circumference (Colin Press-mate blood pressure monitor, Welch Allyn, Arden, USA). Resting blood pressure was taken after 5 minutes of quiet rest, and exercise blood pressure was taken immediately on cessation of the SETT. PP was calculated from the SBP and DBP readings.

QoL and physical activity questionnaires: The New York Heart Association (NYHA) classification, which stratifies patients according to physical activity/exercise limitation, was used in this study to provide a subjective measure of disability. The MLHFQ and HADS questionnaires (Appendices 9 and 10) were used to measure QoL. The MLHFQ was designed to measure the effects of CHF and treatments for CHF on an individual's QoL, and is considered a responsive tool for distinguishing the changes in QoL in patients with CHF (Ni et al, 2000). The HADS Questionnaire is a valid instrument that was recommended by the National Service Framework for Coronary Heart Disease (2000) for the assessment of psychological needs (see Chapter 2 for further details). The National Audit for Cardiac Rehabilitation Physical Activity

questionnaire (see Appendix 11) was used to determine patient exercise/activity levels.

5.5.3 Exercise training protocol

All patients were enrolled in an outpatient supervised exercise training programme where they attended twice per week for 12 weeks; the EI group commenced training immediately following T1, the DI group following T2 (at 12-weeks). The 12-week training programme is described in Chapter 2.

5.5.4 Data analysis

Data analysis was conducted using SPSS version 21.0 and alpha was set at the .05 level. Data were assessed for the normality of their distributions via the Shapiro-Wilk and for homogeneity of variance prior to analysis. The independent t-test was applied to investigate differences in baseline characteristics between the groups where parametric assumptions were met and the Mann Whitney U Test was used for non-parametric data. To measure within-subjects differences and interactions the factorial (mixed) two way ANOVA was applied, with post hoc analysis. A Bonferroni adjustment was performed where appropriate. The Chi-squared (χ^2) test for association compared physical activity levels between groups. Relationships between variables were examined using Pearsons Product Moment (parametric data) or Spearman's Rank Correlation Coefficient (non-parametric data). Data are presented as mean values \pm standard deviation (SD).

5.6 Results

5.6.1 Participants

This final study population consisted of 51 participants; 30 in the EI group and 21 in the DI group. All participants in the EI group completed assessments 1 and 2 (T1 and T2); 26 (87%) completed assessment 3 (T3). In the DI group, all participants completed T1 and T2, and 14 (67%) completed T3. Only 11 of the 21 participants (52%) in the DI group completed the exercise programme following which they completed assessment T2b. There were no adverse events during or as a result of the exercise sessions or during the exercise testing. There were no differences between the groups (Table 5.1) at baseline (T1). Over a quarter of the study participants were female (27%), 78% were NYHA class II and 76% had an underlying history of CHD (MI) attributed as the main aetiological factor. Over half (53%) of the participants were aged 71 to 84 years and resting SBP at T1 ranged from 98 – 167 mmHg for the cohort and DBP 55 – 89 mmHg.

Table 5.1 Baseline participant characteristics

Variable	Early intervention group (n = 30)	Delayed intervention control group (n = 21)
Median age (years)	73 (16)	72 (14) ¹
Baseline BMI (kg/m ²)	30.4 (4.7)	30.9 (6.1) ²
Baseline LVEF%	33 (7)	33 (9) ³
NYHA class (II/III)	22/8	18/3
Gender (m/f)	20/10	17/4
RHR (beat. min ⁻¹)	67 (13)	67 (11)*
CHF cause (IHD/other)	23/7	16/5
Prescribed beta-blocker (%)	97%	100%
Prescribed ACE inhibitor/ARB (%)	97%	90%

Prescribed diuretic (%)	63%	67%
Diagnosed AF (%)	70%	62%
Diagnosed ≥ 1 more co-morbidity (%)	97%	100%

¹ No significant difference between groups ($p = .639$)

² No significant difference between groups ($p = .803$)

³ No significant difference between groups ($p = .871$)

* No significant difference between groups ($p = .903$)

5.6.2 Six-minute walk test performance

Baseline 6MWT distance (Table 5.2): This was the same in both groups ($p = .608$). There were no significant differences in 6MWT distance ($p = .060$) over the trial for both groups. There was, however, a significant interaction effect ($p = .009$)

Walk pace: There were no significant differences in walk pace ($p = .289$) over the trial for both groups. There was a significant difference in walk pace between the groups over the three assessments ($p = .013$). Post hoc analysis showed that, during T2, the EI group walked significantly faster than T1 at minute 2 (T1 67 ± 14 m vs T2

71 ± 17 m; $p = .003$), minute 3 (T1 65 ± 21 m vs T2 70 ± 17 m; $p = .006$), minute 4 (T1 66 ± 18 m vs T2 70 ± 21 m; $p = .005$) and minute 5 (T1 67 ± 16 m vs T2 70 ± 19 m; $p = .004$). The DI group walked significantly slower at minute 5 in T2 (T1 65 ± 16 m vs T2 59 ± 18 m; $p = .021$).

Heart rate: HR increased significantly between minutes 1 and 6 in both groups during T1 (EI group minute 1: 89 ± 9 beat. min⁻¹ vs minute 6: 100 ± 10 beat.

min⁻¹, $p < .0001$; DI group: 88 ± 8 beat. min⁻¹ vs 97 ± 8 beat. min⁻¹, $p = .001$), T2 (EI group minute 1: 85 ± 8 beat. min⁻¹ vs minute 6: 96 ± 8 beat. min⁻¹, $p < .0001$; DI group: 89 ± 8 beat. min⁻¹ vs 100 ± 7 beat. min⁻¹, $p < .0001$) and T3 (EI group minute 1: 87 ± 9 beat. min⁻¹ vs minute 6: 96 ± 10 beat. min⁻¹, $p = .001$; DI group: 87 ± 6 beat. min⁻¹ vs 99 ± 6 beat. min⁻¹, $p = .001$). T2 end of test HR was significantly lower than T1 end of test HR in the EI group and significantly higher in the DI group (Table 5.2).

RPE: There were no between-test differences in RPE values at minutes 1 and 6 ($p = .234$). End of test RPE was significantly higher than RPE at minute 1 in both groups in T1 (EI group minute 1: 11.3 ± 1.1 vs minute 6: 12.7 ± 1.1 , $p < .0001$; DI group: 11.1 ± 1.1 vs 12.7 ± 1.3 , $p = .001$), T2 (EI group minute 1: 11.3 ± 1.2 vs minute 6: 12.8 ± 1.3 , $p < .0001$; DI group: $11.1 \pm .8$ vs $12.9 \pm .7$, $p < .0001$) and T3 (EI group minute 1: 11.3 ± 1.4 vs minute 6: 13.1 ± 1.1 , $p < .0001$; DI group: 11.6 ± 1.1 vs 12.8 ± 1.3 , $p = .014$). End of test RPEs were the same at T1, T2 and T3 in both groups (Table 5.2).

Percentage of heart rate reserve (%HRR): There were no within-subjects differences in %HRR ($p = .934$); however there was a significant interaction effect ($p = .002$). Post hoc analysis showed that there were significant differences in the end of test %HRR during T2 and T3 in both groups compared with T1 (Table 5.2).

Total heart beats: The total number of heart beats (THBs) was calculated for both groups during T1, T2 and T3. There were no significant differences in THBs over the three assessments for both groups ($p = .934$). There was,

however, a significant interaction effect ($p = .029$). Post-hoc analysis with the t-test for related samples (paired t-test) showed that the THBs were lower in the EI group during T2 compared with T1 (Table 5.3).

Heart-rate-walking speed index: There were no between-groups differences in HRWSI in T1, T2 and T3 ($p = .214$). There was a significant difference in HRWSI during T2 and T3 in the EI group compared with T1 (Table 5.3). This equated to a saving of 10 heart beats for every 100 m walked during T2 and 12 heart beats for every 100 m walked during T3.

5.6.3 NT-proBNP levels

Figure 5.1 shows that there were no significant between-groups differences in NT-proBNP plasma levels. There was a significant difference in NT-proBNP levels over the trial for both groups ($p = .020$), but there was no interaction effect ($p = .326$).

Table 5.2 Mean (SD) six-minute walk test performance

	T1 Baseline	T2 12-weeks	T3 6-months
Early intervention group 6MWT distance (m)	398 (100) (n = 30)	423 (108) ¹ (n = 30)	415 (125) (n = 26)
Delayed intervention control group 6MWT distance (m)	384 (95) (n = 21)	379 (93) (n = 21)	366 (152) (n = 14)
Early intervention group HR (bpm) at minute 6	100 (10)	96 (8) ²	96 (10) ²
Delayed intervention control group HR (bpm) at minute 6	97 (8)	100 (7) ³	99 (6)
Early intervention group RPE at minute 6	12.7 (1.1)	12.8 (1.3)	13.1 (1.1)
Delayed intervention control group RPE at minute 6	12.7 (1.3)	12.9 (.7)	12.8 (1.3)
Early intervention group %HRR at minute 6	61 (16)	54 (22) ¹¹	53 (24) ¹¹
Delayed intervention control group %HRR at	57 (17)	70 (15) ²²	67 (18) ²²

minute 6			
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¹ Significantly higher than T1; $p < .0001$

² Significantly lower than T1; $p = .010$

³ Significantly higher than T1; $p = .030$

¹¹ Significantly lower than T1; $p < .035$

²² Significantly higher than T1; $p < .032$

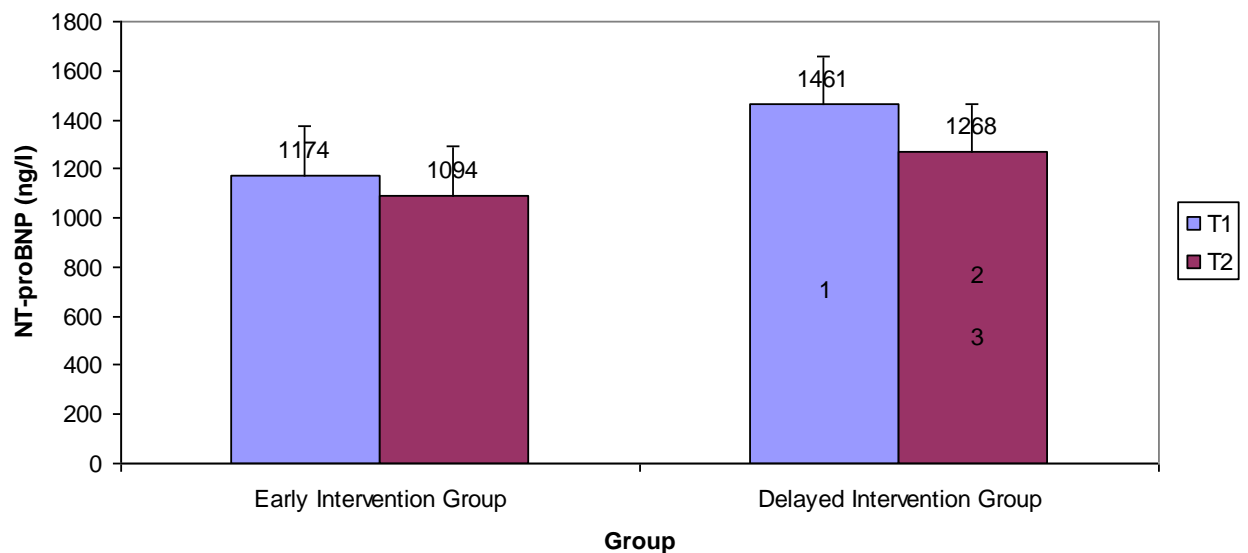
Table 5.3 Mean (SD) total heart beats and heart-rate-walk speed index during the six-minute walk test

	Early intervention group			Delayed intervention control group		
	T1 (n = 30)	T2 (n = 30)	T3 (n = 26)	T1 (n = 21)	T2 (n = 21)	T3 (n = 14)
Total Heart Beats	578 (44)	557 (39) ¹	558 (49)	562 (33)	581 (34)	577 (22)
Heart rate-walk speed index (total heart beats/6MWD x 10 m)	16.3 (7.3)	15.3 (8.7) ²	15.1 (6.9) ³	14.9 (3.2)	15.4 (3.2)	16.1 (6.9)

¹ Significant difference from T1; $p = .004$

² Significant difference from T1; $p < .0001$

³ Significant difference from T1; $p = .028$



¹ No significant between-groups differences

² No significant between-groups differences

³ Significant reduction in NT-proBNP levels over T1 and T2 for both groups (n = 51); p = .020

Figure 5.1 NT-proBNP levels (ng/l) in the early intervention group (post training) and the delayed intervention group (no training) at T1 and T2

5.6.4 Echocardiography

Table 5.4 shows the mean (SD) values of resting LV function of two sub-groups of patients; one from the EI group (n = 10) and one from the DI group (n = 10).

Although there was a statistically significant increase in LV posterior wall thickness the result was not clinically significant.

Table 5.4 Echocardiographic resting LV function in sub-groups

	Early intervention group (n = 10)		Delayed intervention group (n = 10)		p value	
	T1	T2	T1	T2	Within Subjects	Between Groups
LVEF%	41 (10)	41 (8)	40 (13)	41 (13)	.404	.404
EDV (ml)	101 (53)	106 (59)	117 (38)	103 (31)	.442	.097
ESV (ml)	65 (4)	66 (49)	72 (32)	61 (25)	.098	.060
LV thickness septal wall (cm)	1.1 (.30)	1.1 (.25)	1.1 (.18)	1.1 (.16)	.806	.464
LV thickness posterior wall (cm)	.95 (.14)	1.0 (.17) ¹	.99 (.17)	1.1 (.16) ¹	.035	.838
LV internal dimension (cm)	5.3 (.8)	5.2 (.8)	5.5 (.7)	5.4 (.6)	.422	.590

¹ Significantly higher value at T2 for the cohort; $p = .030$

5.6.5 Pulse Pressure

SBP, DBP and PP values remained the same across T1 to T3. PP at rest ranged from 25 – 87 mmHg in the EI group and 32 – 83 mmHg in the DI group. Data were analysed to determine the effect of PP on outcomes at T2 compared with baseline (T1). There were no significant differences in resting and end of test PP, SBP or DBP in T1 and T2 (Table 5.5). There was a very high correlation between resting PP and resting SBP at T1 (EI group: $r = .867$, $p < .0001$; DI group: $r = .856$, $p < .0001$) and T2 (EI group: $r = .799$, $p < .0001$; DI group: $r = .886$, $p < .0001$) but not with DBP (EI group T1: $r = -.114$, $p = .548$, T2: $r = -.070$, $p = .712$; DI group T1: $r = .042$, $p = .857$, T2: $r = .337$, $p = .136$). The relationships between PP and SBP remained at the end of test measurements (EI group T1: $r = .936$, $p < .0001$, T2 $r = .792$, $p < .0001$; DI group T1: $r = .867$, $p < .0001$, T2: $r = .862$, $p < .0001$).

To examine whether PP affected 6MWD, NT-proBNP and MLHFQ score, the EI group and the DI group were each sub-divided to two groups: group 1 < 51 mmHg (mean PP value) and group 2 ≥ 51 mmHg (Table 5.6).

5.6.6 NYHA class and Quality of life

Mean NYHA class reduced significantly in the EI group following exercise training (T2) and at 6-month follow-up (T3), and was significantly lower than mean NYHA class in the DI group at T2 (Table 5.7). There were no between-group differences in NYHA class at T1 ($p = .295$) and T3 ($p = .138$). There were

no significant differences in NYHA class over the three assessments in the DI group.

There were no significant differences or interaction effects in QoL questionnaire scores over the trials (Table 5.8).

Table 5.5 Mean (SD) pulse pressure, systolic and diastolic blood pressure values

	Early intervention group (n = 30)			Delayed intervention control group (n = 21)		
	T1	T2	T1 vs T2 p value	T1	T2	T1 vs T2 p value
Resting PP (mmHg)	51 (14)	51 (13)	.967	51 (16)	53 (19)	.562
End of test PP (mmHg)	60 (21) ¹	59 (21) ¹	.608	64 (19) ¹	60 (21) ¹	.105
Resting SBP (mmHg)	123 (16)	121 (15)	.482	126 (19)	126 (24)	.974
End of test SBP (mmHg)	138 (25) ¹	135 (24) ¹	.462	141 (19) ¹	137 (23) ¹	.133
Resting DBP (mmHg)	72 (8)	70 (7)	.058	74 (10)	73 (11)	.351
End of test DBP (mmHg)	78 (9)	76 (11)	.479	76 (10)	76 (11)	.715

¹ Significantly higher than resting value; p < .014

Table 5.6 Comparison of pre- and post-exercise training outcome measures in patients with a pulse pressure < 51 mmHg compared to a pulse pressure ≥ 51 mmHg

	Early intervention group			Delayed intervention control group		
	Group 1 PP < 51 mmHg (n = 18)	Group 2 PP ≥ 51 mmHg (n = 12)	Between Groups p value	Group 1 PP < 51 mmHg (n = 12)	Group 2 PP ≥ 51 mmHg (n = 9)	Between Groups p value
Mean PP (mmHg)	42 (7)	64 (12)	< .0001	40 (6)	67 (10)	< .0001
6MWD T1 (m)	379 (119)	412 (65)	.538	389 (65)	377 (130)	.862
6MWD T2 (m)	399 (130) ¹	445 (62) ¹	.379	392 (79)	362 (111)	.466
NT-proBNP T1 (ng/l)	1465 (1911)	786 (471)	1.000	1782 (1844)	1034 (846)	.345
NT-proBNP T2 (ng/l)	1285 (1665)	839 (541)	.767	1554 (1536) ²	885 (607)	.422
MLHFQ T1	29 (19)	31 (21)	1.000	29 (13)	40 (24)	.508

MLHFQ T2	26 (24)	28 (25)	.884	26 (14)	39 (19)	.129
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¹ Significantly higher than T1, $p < .043$

² Significantly lower than T1, $p = .023$

Table 5.7 Mean (SD) NYHA class

	Early intervention group			Delayed intervention control group		
	T1 (n = 30)	T2 (n = 30)	T3 (n = 26)	T1 (n = 21)	T2 (n = 21)	T3 (n = 14)
NYHA	2.3 (.5)	1.8 (.6) ¹	1.7 (.7) ¹	2.0 (.6)	2.1 (.3) ²	2.0 (.6)

¹ Significantly lower than T1; $p < .0001$

² Significantly higher than Early intervention group; $p = .011$

Table 5.8 Mean (SD) anxiety, depression and MLHFQ scores

	Early intervention group			Delayed intervention control group			p values mixed ANOVA	
	T1 (n = 30)	T2 (n = 30)	T3 (n = 26)	T1 (n = 21)	T2 (n = 21)	T3 (n = 14)	Within Subjects p value	Interaction Effect p value
Anxiety	7 (4)	6 (4)	7 (4)	5 (4)	5 (4)	5 (3)	.448	.254
Depression	4 (3)	4 (3)	4 (3)	4 (3)	4 (3)	3 (3)	.564	.537
MLHFQ score	31 (20)	29 (23)	30 (24)	26 (12)	23 (12)	20 (13)	.244	.402

Figure 5.2 shows the number of participants in each group who reported being physically active for 30 minutes on at least five days of the week at T1, T2 and T3. There was a significant association between groups and physical activity at T1 ($\chi^2(1) = 5.063$; $p = .024$) and T2 ($\chi^2(1) = 4.073$; $p = .044$).

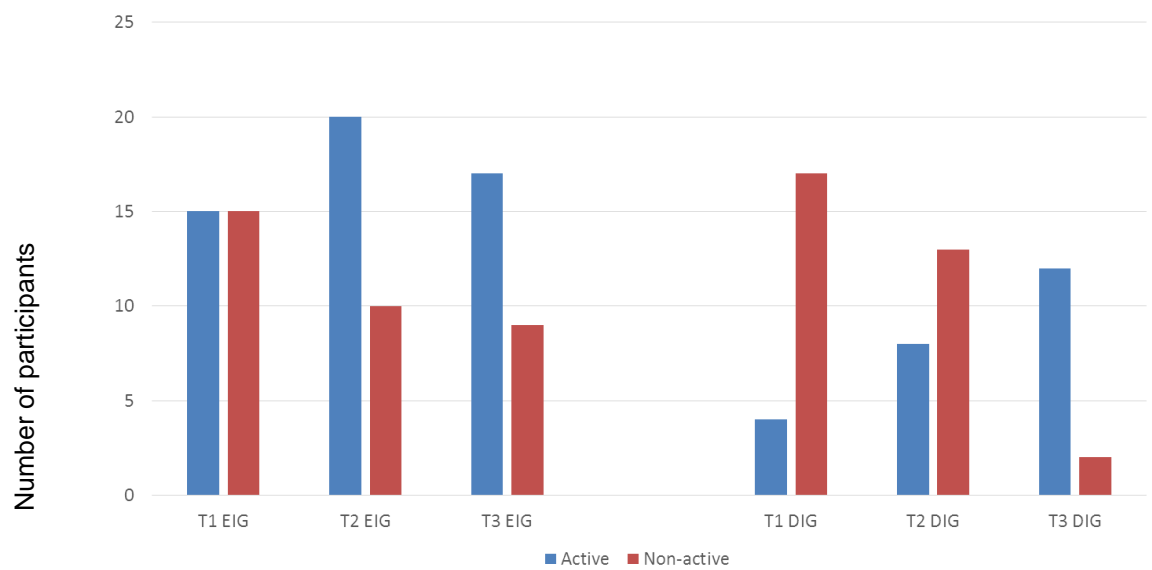


Figure 5.2 The number of participants in each group who reported being physically active for 30 minutes on at least five days of the week at T1, T2 and T3

5.6.7 Correlations

At baseline, correlation analyses on corresponding variables of 6MWD, NT-proBNP level, BMI, age LVEF%, MLHFQ score and PP were performed for the cohort. There were significant inverse correlations between 6MWD and NT-proBNP ($r = -.364$; $p = .009$), BMI and age ($r = -.352$; $p = .011$) and PP and age ($r = -.307$; $p = .029$).

Further correlation analyses were performed for the differences between the values in T1 and T2. Results are detailed in Tables 5.9 and 5.10.

Table 5.9 Correlations of key measures in the Early intervention group

	Δ6MWD	ΔHRWSI	ΔMLHFQ score	ΔNYHA class	ΔNT-ProBNP
Δ6MWD (m)		$r = -.707$ $p < .0001^*$	$r = -.128$ $p = .500$	$r = -.241$ $p = .199$	$r = -.151$ $p = .426$
ΔHRWSI	$r = -.707$ $p < .0001^*$		$r = .199$ $p = .310$	$r = .257$ $p = .186$	$r = .109$ $p = .583$
ΔMLHFQ score	$r = -.128$ $p = .500$	$r = .199$ $p = .310$		$r = -.031$ $p = .871$	$r = .078$ $p = .681$
ΔNYHA class	$r = -.241$ $p = .199$	$r = .257$ $p = .186$	$r = -.031$ $p = .871$		$r = .367$ $p = .046^*$
ΔNT-proBNP (ng/l)	$r = -.151$ $p = .426$	$r = .109$ $p = .583$	$r = .078$ $p = .681$	$r = .367$ $p = .046^*$	

* Significant correlation

Table 5.10 Correlations of key measures during the control period in the Delayed intervention group

	Δ6MWD	ΔHRWSI	ΔMLHFQ score	ΔNYHA class	ΔNT-ProBNP
Δ6MWD (m)		$r = -.731$ $p < .0001^*$	$r = -.231$ $p = .313$	$r = .372$ $p = .097$	$r = .212$ $p = .356$
ΔHRWSI	$r = -.731$ $p < .0001^*$		$r = .025$ $p = .918$	$r = -.339$ $p = .144$	$r = -.336$ $p = .112$

ΔMLHFQ score	r = -.231 p = .313	r = .025 p = .918		r = .296 p = .193	r = .037 p = .873
ΔNYHA class	r = .372 p = .097	r = -.339 p = .144	r = .296 p = .193		r = .074 p = .750
ΔNT-proBNP (ng/l)	r = .212 p = .356	r = -.336 p = .112	r = .037 p = .873	r = .074 p = .750	

* Significant correlation

5.6.8 Effect of delayed rehabilitation on uptake and functional capacity

After completing T2, participants in the DI group were invited to join the exercise training programme (following a delay of 12 weeks). Eleven patients (52%) completed the 12-week programme and attended for a further assessment (T2b). 6MWD increased (Table 5.11), there was a significant decrease in end of test HR (T2 92 ± 8 beat. min⁻¹ vs T2b 87 ± 6 beat. min⁻¹; p = .05), THBs (Table 5.11) and HRWSI (Table 5.11) at the same RPE (T2 $13 \pm .7$ vs T2b 13 ± 1 ; p = .414). NYHA class also improved (T2 2 ± 0 vs T2b $1.7 \pm .4$; p = .038). At T3 the results remained the same as at T2b.

Table 5.11 Mean (SD) 6MWT distance, total heart beats and heart-rate-walk speed index in the 11 participants of the Delayed intervention group who completed the 12-week exercise training programme

	T2 (after 12-weeks of no training)	T2b (post 12-weeks exercise training)	T3 (6-month follow-up)
	(n = 11)	(n = 11)	(n = 11)
6MWD (m)	393 (85)	431 (83) ¹	412 (104)
Total Heart Beats	585 (38)	566 (25) ²	573 (19)

Heart-rate-walk speed index (total heart beats/6MWD x 10 m)	15.5 (3.6)	13.6 (2.8) ³	15.0 (5.3)
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¹ Significantly higher than T2; $p = .002$

² Significantly lower than T2; $p = .018$

³ Significantly lower than T2; $p = .002$

5.7 Discussion

This study characterises the responses of CHF patients referred to a moderate intensity CR exercise training programme, and uses recommended outcome measures to demonstrate the effectiveness of this intervention. The demographic data collected in this current study compare favourably with reported data (British Society of Heart Failure, 2013). National Guidelines (NICE, 2010) and key systematic reviews (Rees et al., 2004; Piepoli et al. 2004; Davies et al., 2010; Taylor et al., 2014) have reported exercise training to be safe in young, predominantly male CHF populations, with little or no co-morbidities. This study confirms that a moderate intensity exercise training programme, following UK standards and guidelines, is safe for CHF populations that are typical of those attending UK CR centres.

6MWT performance: Following exercise training in EI group, the mean increase in 6MWT distance was statistically significant (25 ± 35 m; $p < .0001$). However, this change has been reported not to be of clinical significance as noted by the similar distance changes reported by Shoemaker et al., (2012). They deemed an increase of 45m was required to be of a significant influence in aerobic capacity and QoL. Whilst it could be claimed the distance walked was not clinically significant, physiologically the patients had improved because they

were walking at a faster pace for given RPE (~12) but with significantly lower heart rates (Table 5.2). During the 6MWT, patients did show signs of fatigue as demonstrated by the upward drift in RPE from minute 1 to minute 6, confirming the findings of Study 1. The relationship between heart rate and walking speed, as described by the HRWSI, may therefore provide an additional perhaps more physiologically precise marker of change compared to a simply reporting of distance walked (HRWSI EI group: T1 16.3 ± 7.3 vs T2 15.3 ± 8.7 heart beats per 10 m walked, $p < .0001$). These findings support the suggestion that the 6MWT distance alone may not be sensitive to changes in functional capacity (McKelvie et al., 2002). Attitudes, mood and motivation all influence performance in walking speed and distance covered (Guyatt et al., 1985). It is therefore recommended that the combined use of the HRWSI and 6MWT distance is used to report meaningful changes in the 6MWT as highlighted in Tables 5.2 and 5.3. The exercise-induced benefits remained at 6-month follow-up (T3) in the EI group for 6MWD, %HRR and HRWSI. In conclusion, in a representative sample of the UK CHF population, by applying current UK guidelines, a 12-week programme of exercise training results in an improved functional capacity.

NT-proBNP: This study demonstrated that, despite the significant improvement in functional capacity in the EI group (increased 6MWT distance at a lower HR, lower %HRR and improved HRWSI), there were no significant changes in NT-proBNP levels (-75 ± 401 ng/l; $p = .381$) following a 12-week exercise training programme. Similarly, Nilsson et al. (2010) reported significantly improved walking distances without significant changes in NT-proBNP levels. In

accordance with the current study they found no significant correlation between Δ NT-proBNP and Δ 6MWD in spite of a significant inverse correlation between baseline 6MWD and NT-proBNP ($r = -.24$; $p = .035$). The authors suggested that improvements in functional capacity may have been too small to influence NT-proBNP levels and that the peripheral changes that occur following exercise training (such as improved capillarisation, increased number and size of mitochondria and increased oxidative enzyme activity), which lead to improvements in functional capacity, do not affect NT-proBNP levels. This speculation corresponds with the small improvements in 6MWD seen in this study.

The results of the current study support the suggestion that NT-proBNP is not a reliable marker for measuring changes in functional capacity in a stable CHF population with optimal medical treatment (Meyer et al., 2004; Nilsson et al. 2010). The participants in the current study were representative of the population attending CR programmes in the UK (British Society for Heart Failure, 2013), whereas other studies that have demonstrated the positive effects of exercise training on natriuretic peptides likely produced divergent results due to differences in the population, the mode and the duration of exercise. It is worth noting the paper by Koglin et al. (2001) which discussed the important protective role of BNP in delaying the progression of CHF. The authors refer to studies that used an infusion of synthetic BNP, which resulted in a rapid and sustained improvement of the patient's clinical status and suggested a possible relationship between increased BNP levels, impaired BNP activity and mortality in CHF. This would support the proposals by Mangiafico et al. (2013) who reported a lack of mature plasma BNP in its protective form in

patients with CHF, plus the presence of less biologically active precursors and degraded forms of BNP. The authors referred to a study by Miller et al. (2011) who proposed that the BNP that is detected by clinical assays is actually degradation products and less active forms of BNP.

LV function: It was not possible to follow the echocardiogram protocol in its entirety due to the incidence of atrial fibrillation in the cohort, making such an evaluation difficult. Furthermore the availability of equipment meant that several echocardiography parameters could not be measured. The NT-proBNP findings in the EI group are supported by the results of the echocardiograms which indicated that there were no significant changes in LV dimension or LVEF, previously reported as a contributory factor to changes in NT-proBNP levels (Rengo et al., 2014). The echocardiogram findings are in accordance with those of Giannuzzi et al. (2003), Giallauria et al. (2008) and Haykowsky et al. (2007) who reported that exercise training of less than 6-months duration does not reverse remodelling. In summary, in a representative sample of the UK CHF population, by applying current UK guidelines, a 12-week programme of exercise training did not result in a reduction in plasma BNP levels and an associated improvement in LV function.

Pulse pressure: The results of this study demonstrate that the benefits CHF patients derive from participating in a CR programme are not negatively influenced by baseline PP, confirming previous findings (Leslie and Buckley, 2012). There was a significant correlation between resting PP and SBP at both T1 (EI group $r = 0.867$, $p < .0001$; DI group $r = .856$, $p < .0001$) and at T2 (EI

group $r = .799$, $p < .0001$; DI group $r = .886$, $p < .0001$) but not between PP and DBP at either assessment. This indicates that, in this cohort, PP levels were closely linked to SBP, indicative of cardiac output (Franklin et al., 1999), and that the possible variability in DBP was lower than that of SBP. Regardless of resting levels, SBP increased appropriately during exercise whilst DBP remained unchanged, leading to a corresponding increase in PP. Exercise training did not influence resting levels or end of test levels of SBP or PP at T1, T2 and T3.

NYHA class and QoL: NYHA class improved significantly (it was lower) in the EI group ($p < .0001$) and at T2 was significantly lower than the DI group ($p = .011$). Furthermore there was a significant correlation (though somewhat low) between Δ NYHA class and Δ NT-proBNP in the Early intervention group ($r = .367$, $p = .046$) suggesting some link between changes in NT-proBNP and NYHA class. NYHA score also improved in the DI cohort who completed the exercise training programme (T2 2 ± 0 vs T2b $1.7 \pm .4$; $p = .038$). HADS scores did not improve in either group, which echoes the findings reported in two other studies using this questionnaire (Radzewitz et al., 2002; Witham et al., 2012). Despite the reported prevalence of depression in patients with CHF (Rutledge et al., 2006), the baseline scores were not indicative of any clinical signs of anxiety or depression in either group which probably explains why there were no changes in HADS. Smart et al. (2011) reported that clinicians should expect a reduction of approximately 10 points on the MLHFQ, but the scores at T1, T2 and T3 were unchanged in this study. Similar to HADSs, the baseline scores were relatively low (good), which could have caused a basement effect. The

mean scores were < 30% of the maximum score possible (105 points). This could be a result of the patients already being optimised on their CHF medication and stable prior to recruitment, thereby improving QoL prior to recruitment. Self-reported levels of physical activity were higher in both groups at T2 and T3 compared with T1, suggesting that anything from a brief intervention with a health care professional to a 12-week exercise programme can influence behaviour change. In conclusion, in a representative sample of the UK CHF population performing 12 weeks exercise training in keeping with UK guidelines, results in an improvement in QoL demonstrated by the improvements seen in NYHA class and self reported levels of physical activity.

Correlation between changes in functional capacity, with changes in plasma BNP levels and changes in QoL: As summarised in Tables 5.9 and 5.10 changes in functional capacity were not related to any changes in either cardiac biomarkers, LV function or QoL. The intensity of the exercise may have been a factor, where in most other studies (cited in systematic reviews) demonstrating such changes, the participants were younger, with fewer co-morbidity and working at higher intensities. Therefore, in a representative sample of the UK CHF population participating in a 12-week programme of exercise in keeping with UK guidelines relevant to age and co-morbidity, does not have an influence on either plasma BNP levels or QoL.

Effects of delaying cardiac rehabilitation: The DI group achieved similar outcomes on completion of the exercise training programme following a delay of 12 weeks, which is reassuring. The drop-out rate was high, however. Only 48%

of participants in the DI group completed the 12-week course following assessment T2. The high drop-out rate concurs with the findings of Parker et al. (2011) who reported that early access to CR following acute ST-elevation myocardial infarction resulted in a 3-fold increase in patient participation. Delaying commencement of CR reduces the number of patients who could benefit, which supports the evidence and the goals cited by the BACPR (Buckley et al., 2013).

5.8 Limitations

Rate of referral and group capacity were the main limiting factors for the sample size for this study and thus the small numbers may have affected the results, nonetheless the overall results are encouraging. The mode of exercise and the intensity of training differed to those used in many of the published reviews and meta-analyses.

In addition the CHF population recruited to the current study was more representative of patients attending CR programmes in the UK. The results from the current study may therefore not be comparable with previously published studies.

5.9 Conclusion

For a given physiological strain, this group of optimally medical treated patients with CHF improved in physical function (6MWD and HRWSI) with a corresponding improvement in their perceived functional ability (NYHA functional class). There were no adverse events during or as a result of the exercise sessions or during the exercise testing, which concurs with the

National Guidelines (NICE, 2010) and key systematic reviews (Rees et al., 2004; Piepoli et al. 2004; Davies et al., 2010; Taylor et al., 2014) and training did not adversely affect cardiac function. Delaying the start of supervised exercise training had a detrimental effect on uptake and compliance but not outcomes. Despite the significant improvement in functional capacity following moderate intensity exercise training, no significant changes in NT-proBNP were found in the EI group. NT-proBNP measurement in this cohort appears to be of limited value, suggesting that exercise training at moderate intensity is unable to significantly influence the neurohormonal burden associated with CHF. This area requires further study on a greater number of patients, to confirm exercise intensities that will produce both clinically and statistically significant outcomes. The findings of this study support the value of exercise-based rehabilitation for patients with CHF and reinforce the importance of offering timely access to supervised exercise training programmes for all patients diagnosed with stable CHF.

Chapter 6

General Discussion

6.1 Overview

Often, studies such as this are undertaken in a non-clinical research environment, with access to far more resources than a routine clinical setting would allow in the UK. Access to equipment and facilities such as those used in large clinical trials was limited, unlike Europe and the US, as was capacity for supervised exercise sessions. Although the number of eligible patients was also limited, the uptake in the UK is actually far greater than in Europe and the US (NACR, 2013). The standard operating procedures that are followed within the Royal Wolverhampton Trust resulted in lengthy delays, initially in recruitment then later impeding the use of equipment on loan from the University of Chester. Support from other areas such as Clinical Chemistry, the Respiratory Centre and Cardiac Investigations Department was available, which proved invaluable.

These clinically-based and ecologically valid studies, although generating several challenges, have led to several novel research findings. In addition they have confirmed previously reported findings.

6.2 Main findings

6.2.1 An alternative to the 6MWT practice

The 6MWT is frequently recommended for patients with CHF due to it being a self-paced, sub-maximal test that has proven reliability and validity in CHF. A practice 6MWT test is recommended in both clinical practice and in research to increase the reliability of the test by aiming to filter out influences of familiarisation, pacing and motivation on final outcome tests. The effects of fatigue on walking performance, based on the increasing RPE values during the 6MWT (Chapters 3 and 5), are of concern. Furthermore, in clinical practice a practice test proves to be time consuming. Study 1 verified the efficacy of a two-minute practice walk in a small cohort of patients with CHF. Actual baseline 6MWT distance walked in Grp1-2min was not significantly different (345 ± 83 m vs 329 ± 96 ; $p = .212$) to the distance predicted from the mean distance walked during the two minute practice (115 ± 28 m). Effects of pacing or fatigue on walking pace were assessed between practice and baseline 6MWT using a bias \pm 95% limits of agreement (LoA) analysis. In Grp1-2min mean walking pace during minute 2 of the practice test was 57.5 ± 3.8 m.min⁻¹ and during the baseline 6MWT 57.8 ± 14.7 m.min⁻¹. Walking pace was not different (95%LoA $p = .823$) between the practice and 6MWT. Thus both a two-minute and a six-minute practice test were equally effective in predicting baseline 6MWD in this cohort of patients with CHF. This data have provided preliminary evidence that a two-minute practice test saves valuable clinical assessment time and is as effective in influencing pacing as a six-minute practice walk for CHF patients being assessed by a 6MWT, whilst reducing risk of fatigue seen in a 6MWT.

6.2.2 Further validation of an adapted Chester step test in CHF

Although the 6MWT is recommended for patients with CHF, it requires a significant amount of space. Study 2 (Chapter 3b) demonstrated that a low (4-inch) step test is a valid alternative to the 6MWT, particularly where space might be an issue. The similarity between CST1 and CST2 for HR, RPE and total number of steps indicated that the CST is reproducible in CHF patients. Noteworthy in this study were the HR and VO_2 responses to incremental exercise in this clinical population. HR was reliable on a test re-test basis, but its validity in this study was challenged as an indicator of oxygen uptake response and kinetics. Typically, validity is measured against VO_2 max; however this study questions the validity of estimates of VO_2 max/peak and METs when METs estimates are based on 3.5 ml/kg/O_2 being equal to 1 MET (Buckley et al., 2004). Resting VO_2 value was 2.8 ml/kg/O_2 in this cohort of patients with CHF. Actual VO_2 measures were suggestive of altered oxygen kinetics and HR rise was blunted, all of which is in keeping with previous evidence of incremental exercise testing responses in CHF. HR rise over the course of the three-minute stages was not proportionate to the rise in VO_2 . VO_2 continued to rise into the third minute, which showed the delayed oxygen kinetics.

CST2 duration ranged from 5 minutes to 12 minutes, thus the total exercise time in the majority of patients was sufficient and useful for assessing cardiorespiratory responses (American Thoracic Society, 2003). The CST, designed and validated for use in healthy subjects, uses two-minute stages when applied according to the manual. It seems, however, that three minutes at

each stage, as used in this study, may have also been insufficient to allow appropriate HR responses in this cohort and so further studies to determine the optimum duration for each stage are recommended.

6.2.3 Acute and chronic responses of NT-proBNP to exercise

Examination of the acute response of NT-proBNP levels to moderate intensity exercise revealed individual variability that is worthy of further investigation. From the sub-group analysis it appears that patients with baseline NT-proBNP levels ≥ 1000 ng/l fail to release NT-proBNP in response to acute exercise, therefore further investigation of CHF patients with high levels of circulating natriuretic peptides are warranted. Furthermore, it appears from the results of the main clinically-based study that the current CR exercise prescription guidelines (12-weeks of exercise training at 40 – 60% HRR) do not achieve those NT-proBNP results and associated changes in LV function seen in published meta-analyses. This suggests that the recommended intensity is too low and the frequency insufficient to result in a clinically significant reduction in NT-proBNP levels post training despite the observed improvements in functional capacity and NYHA class. The use of highly sensitive equipment in future studies may increase our understanding of the acute physiological responses to exercise.

6.2.4 Functionality

Although the increase in 6MWT distance in the EI group (25 ± 35 m; $p < .0001$) was not considered to be of clinical significance within the limits of variability

and reliability of the tool, the statistically significant increase was associated with a lower HR and %HRR at the same RPE. Furthermore there was a significant improvement in the HRWSI compared to T1. This clearly demonstrated that training resulted in an improvement in physical function. Patients in the DI group also achieved similar outcomes when they completed training, indicating that patients can still benefit from exercise even after a 12-week delay prior to commencing supervised exercise training. The use of HRWSI demonstrates a new step in reporting 6MWT performance.

6.2.5 Pulse pressure

Patients with CHF often have low PP due to low SBP (a result of reduced stroke volume) and normal DBP, and may exhibit a reduced cardiac output response to exercise (Wilson et al., 1996). The main intervention study (Chapter 5) confirmed the initial findings of a preliminary retrospective study (Leslie and Buckley, 2012), which revealed that patients with CHF do benefit from CR regardless of PP. Thus it appears that PP neither limits nor influences improvements in exercise capacity and QoL in patients with CHF. Furthermore, a course of exercise training does not affect PP.

6.2.6 Quality of life

NYHA class improved (T1 $2.3 \pm .5$ vs T2 $1.8 \pm .6$; $p < .0001$) following exercise training; however there were no significant changes in HADS and MLHFQ scores.

6.2.7 Correlation between changes in functional capacity, with changes in plasma BNP levels and changes in QoL

Δ NYHA class correlated with Δ NT-proBNP levels following exercise training and there was a significant negative correlation between Δ 6MWT distance and Δ HRWSI ($r = -.707$, $p < .0001$). A significant negative correlation was also found in the DI group, between Δ 6MWT distance and Δ HRWSI ($r = -.731$, $p < .0001$). This demonstrates the worth of using HRWSI to emphasise small changes in functional capacity that might be of significant benefit to CHF patients.

6.3 Recommendations for practice

This study demonstrates that a 12-week course of moderate intensity exercise increases functional capacity but has little effect on NT-proBNP. When there has been a reported change in natriuretic peptides it appears to be in studies using a higher exercise intensity (i.e. above ventilatory threshold). The first ventilatory threshold has been proposed as the maximum training intensity for the CHF population; however emerging evidence suggests that it might be possible to train CHF patients above this threshold without additional risk. Indeed, CHF patients have been reported to exercise at a high percentage of VO_2 peak during a sub-maximal 6MWT (Faggiano et al., 1997). Furthermore, they are known to perform activities of daily living at a higher percentage of their VO_2 peak compared to healthy individuals (Giannuzzi et al., 2001). It seems, therefore, that patients with stable NYHA class I to II and perhaps in class III are able to exercise safely at intensities equal to the first ventilatory threshold (Carvalho and Mezzani, 2011). Indirect measures of exercise intensity assessment and prescription used routinely in CR settings, however, have

several limitations. Absolute exercise intensity can only be determined by carrying out a CPET and thus it appears that CPET may be advisable in order to avoid inadequate exercise prescription. This would prove impractical and even impossible for most CR providers in a clinical setting. More practical measures, such as 6MWT, cycle ergometer tests and step tests are used in clinical practice. Chronotropic incompetence and altered oxygen kinetics make interpretation of the findings of both maximal and sub-maximal exercise tests difficult.

Additionally, the guidelines regarding lower intensity limits lack standardisation and, certainly from the results of this study, it appears that the recommended training intensities are not sufficient to bring about the results seen in published reviews and meta-analyses. Emerging evidence suggests that high intensity interval training is safe for CHF patients, thus making the prescription of a specific aerobic training intensity complex for CR clinicians. Research in the field of exercise training for elderly CHF patients with existing co-morbidities should focus on the development of appropriate evidence-based guidelines and standards for exercise prescription, complimented by clinical evaluation and risk assessment of exercise-related adverse event.

6.4 Future research

A significant number of patients with CHF are elderly, female and many are frail, with a substantial burden of co-morbid disease. Many of the CHF participants recruited into exercise training trials were young, male, and had little co-morbid disease. It remains to be confirmed whether the outcomes of the relatively high

intensity exercise programmes that have been reported in the meta-analyses can be successfully applied to older, female and frail patients who routinely attend CR in the UK. Similarly, the diagnosis of heart failure with preserved ejection fraction is becoming more commonplace and again it is not clear whether the results of trials that recruited patients with poor LVEF are transferrable to this population.

Neurohormonal factors are predictive of survival in CHF when measured at rest, and measurement of natriuretic peptides appears to be a superior prognostic marker than other parameters such as LVEF (Lainchbury and Richards, 2012). The additional measurement of natriuretic peptide concentrations and their response to exercise may be valuable. The results presented in Chapter 5 suggest that further research is warranted to measure acute serial changes in natriuretic peptide levels using high-sensitivity equipment following exercise. This may establish clear recommendations regarding the frequency and intensity of exercise sessions for patients with CHF; as yet it appears that 'rest days' are not essential. Measurement of natriuretic peptides following a course of exercise at a selection of intensities may help establish clearer guidelines regarding exercise prescription, and link to function, QoL and survival.

6.5 Conclusion

Preliminary findings suggest that a two-minute practice walk prior to a 6MWT can reliably predict pace and 6MWT distance, and reduce the risk of fatigue seen during a full 6MWT. The additional use of HRWSI demonstrates a new

step in reporting 6MWT performance. This technique is particularly useful as small improvements in functional capacity, demonstrated by an increased 6MWT distance, seen in routine clinical practice can often have a significant impact on perceived QoL. These small improvements are repeatedly considered insignificant in published studies. Where space is limited an adapted low (4-inch) CST is a reliable alternative to the 6MWT. Further testing is recommended to confirm the optimum duration for each stage due to the altered oxygen kinetics seen in patients with CHF.

The participants recruited to this study are not comparable with the majority recruited to published individual studies and systematic reviews, and the median age is not as old as that reported in the recent national heart failure audit (British Society of Heart Failure, 2013); however they are more representative of the CHF population attending UK-based CR programmes (NACR, 2013). The findings reported in Chapter 5 are reassuring but in order for all patients to fully realise the benefits of exercise training, we need to design and study exercise programmes that are at an appropriate exercise intensity for elderly, frail and female patients, rather than the atypical minority of young, male CHF patients studied to date. The participants recruited to this current study all had confirmed LVSD, but we must also consider those with preserved ejection fraction and thereby establish clear, effective exercise prescription guidelines for CHF-rehabilitation programmes. Delaying the start of CHF-rehabilitation did not affect the outcomes for those patients in the DI group who completed the 12-week course; however the delay clearly affected uptake and adherence. To ensure that all patients benefit from supervised exercise by

making the transition from referral to actual attendance, clinicians must offer early access to CR.

References

Ainsworth BE, Haskell WL, Leon et al. Compendium of physical activities: energy costs of human movement. *Medicine and Science in Sports and Exercise* 1993; 25: 71 – 80

American College of Sports Medicine. Guidelines for exercise testing and prescription 6th Edition. Lippincott Williams and Wilkins. 2000

American College of Sports Medicine. Guidelines for exercise testing and prescription 7th Edition. Lippincott Williams and Wilkins. 2007

American College of Sports Medicine. ACSM's health-related physical fitness assessment manual 2nd Edition. Baltimore: Lippincott Williams & Wilkins. 2008

American Thoracic Society statement: guidelines for the six-minute walk test. ATS Committee on Proficiency Standards for Clinical Pulmonary Function Laboratories. *American Journal of Respiratory and Critical Care Medicine* 2002; 166(1): 111 – 117

American Thoracic Society; American College of Chest Physicians. ATS/ACCP statement on cardiopulmonary exercise testing. *American Journal of Respiratory and Critical Care Medicine* 2003; 167(2): 211 – 277

Anker SD and von Haehling S. Inflammatory mediators in chronic heart failure: an overview. *Heart* 2004; 90: 464 – 470

Aronson D, Burger AJ. Relation between pulse pressure and survival in patients with decompensated heart failure. *American Journal of Cardiology* 2004; 93: 785 – 788

Association of Chartered Physiotherapists in Cardiac Rehabilitation. Standards for the exercise component of the phase III cardiac rehabilitation. 2009

Austin J, Williams R, Ross L, Moseley L and Hutchinson S. Randomised controlled trial of cardiac rehabilitation in elderly patients with heart failure. *European Journal of Heart Failure* 2005; 7(3): 411 – 417

Beale L, Carter H, Doust J, Brickley G, Silberbauer J and Lloyd G. Exercise heart rate guidelines overestimate recommended intensity for chronic heart failure patients. *British Journal of Cardiology* 2012; 17(3): 133 – 137

Belardinelli R, Georgiou D, Scocco V, Barstow TJ and Purcaro A. Low intensity exercise training in patients with chronic heart failure. *Journal of the American College of Cardiology* 1995; 26(4): 975 – 82

Belardinelli R, Georgiou D, Cianci G and Purcaro A. Randomized, controlled trial of long-term moderate exercise training in chronic heart failure: effects on functional capacity, quality of life and clinical outcome. *Circulation* 1999; 99: 1173 – 1182

Belardinelli R, Georgiou D, Cianci G and Purcaro A. 10-year exercise training in chronic heart failure: a randomized controlled trial. *Journal of the American College of Cardiology* 2012; 60: 1521 – 1528

Benetos A, Zureik M, Morcet J, Thomas F, Bean K, Safar M, Ducimetière P and Guize L. A decrease in diastolic blood pressure combined with an increase in systolic blood pressure is associated with a higher cardiovascular mortality in men. *Journal of the American College of Cardiology* 2000; 35(3): 673 – 680

Bettencourt P, Ferreira A, Dias P, Pimenta J, Friões F, Martins L and Cerqueira-Gomes M. Predictors of prognosis in patients with stable mild to moderate heart failure. *Journal of Cardiac Failure* 2000; 6: 306 – 313

Bittner V, Weiner D, Yusuf S, Rogers WJ, McIntyre KM, Bangdiwala SI, Kronenberg MW, Kostis JB, Kohn RM, Guillotte M, Greenberg B, Woods PA and Bourassa MG. Prediction of mortality and morbidity with a 6-minute walk test in patients with left ventricular dysfunction. *Journal of the American Medical Association* 1993; 270: 1702 – 1707

Blacher J and Safar ME. Large-artery stiffness, hypertension and cardiovascular risk in older patients. *Nature Clinical Practice Cardiovascular Medicine* 2005; 2(9): 450 – 455

Bland JM and Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. *Lancet* 1986; 1(8476): 307 – 310

Bonow RO. New insights into the cardiac natriuretic peptides. *Circulation* 1996; 93: 1946 – 1950

Borg GAV. Borg's Rating of Perceived Exertion and Pain Scales. IL; *Human Kinetics* 1998

British Association for Cardiac Rehabilitation Guidelines for Cardiac Rehabilitation. Blackwell Science Ltd 1995. Reprinted 2000

British Association for Cardiac Prevention and Rehabilitation Standards and Core Components for Cardiovascular Disease Prevention and Rehabilitation 2012 (2nd Edition)

British Society for Heart Failure National Heart Failure Audit Report, NICOR website, <http://www.ucl.ac.uk/nicor/audits/heartfailure/additions/files> [accessed 07/11/2014]

Brooks D, Parsons J, Hunter JP, Devlin M and Walker J. The 2-minute walk test as a measure of functional improvement in persons with lower limb amputation. *Archives of Physical Medicine and Rehabilitation* 2001; 82(10): 1478 – 1483

Brooks D, Parsons J, Tran D, Jeng B, Gorczyca B, Newton J, Lo V, Dear C, Silaj E and Hawn T. The two-minute walk test as a measure of functional capacity in cardiac surgery patients. *Archives of Physical Medicine and Rehabilitation* 2004; 85(9): 1525 – 30

Brubaker PH and Kitzman DW. Chronotropic incompetence: causes, consequences, and management. *Circulation* 2011; 123(9): 1010 – 1020

Brubaker PH, Moore JB, Stewart KP, Wesley DJ and Kitzman DW. Endurance exercise training in older patients with heart failure: results from a randomized, controlled single-blind trial. *Journal of the American Geriatrics Society* 2009; 57(11): 1982 – 1989

Buckley JP. A critique on measuring reliability in exercise tests and outcome measures. *European Journal of Preventive Cardiology* 2011; 19(1): 41 – 42

Buckley JP and Borg GA. Borg's scales in strength training; from theory to practice in young and older adults. *Applied physiology, nutrition and metabolism* 2011; 36(5): 682 – 692

Buckley J and Eston RG (2007) in Winter EM, Jones AM, Davison RRC, Bromley PD and Mercer TH (editors). British Association of Sport and Exercise Sciences. Sport and Exercise Physiology Testing: Guidelines. Volume 1: Sports Testing. The British Association of Sport and Exercise Sciences Guide. London: Routledge 2007

Buckley JP, Eston RG, Sim J. Ratings of perceived exertion in Braille: validity and reliability in production mode. *British Journal of Sports Medicine* 2000; 34: 297 – 302

Buckley JP, Furze J, Doherty P, Speck L, Connolly S, Hinton S, Jones JL on behalf of BACPR. BACPR scientific statement: British standards and core components for cardiovascular disease prevention and rehabilitation. *Heart* 2013; 99: 1069 – 1071

Buckley JP, Holmes J and Mapp G. Exercise on Prescription. Cardiovascular activity for health. Oxford: Butterworth Heinemann 1999

Buckley JP, Reardon M, Innes G and Morris M. Using a heart-rate walking speed index to report truer physiological changes when using walking performance tests in cardiac rehabilitation. *Journal of Cardiopulmonary Rehabilitation and Prevention* 2010; 30: 346 – 347 (abstract)

Buckley JP, Sim J and Eston RG. Reproducibility of ratings of perceived exertion soon after myocardial infarction: responses in the stress-testing clinic and the rehabilitation gymnasium. *Ergonomics* 2009; 52(4): 421 – 427

Buckley JP, Sim J, Eston RG, Hession R and Foc R. Reliability and validity of measures taken during the Chester step test to predict aerobic power and to prescribe aerobic exercise. *British Journal of Sports Medicine* 2004; 38: 197 – 205

Butland RJ, Pang J, Gross ER, Woodcock AA, Geddes DM. Two-, six- and 12-minute walking tests in respiratory disease. *British Medical Journal* (Clin Res Ed) 1982; 284(6329): 1607 – 1608

Butterfield JA, Faddy SC, Davidson P and Ridge B. Exercise training in patients with stable chronic heart failure. *Journal of Cardiopulmonary Prevention and Rehabilitation* 2008; 28(1): 33 – 37

Cahalin LP, Mathier M, Semigran MJ, Dec GW and DiSalvo TG. The 6-min walk test predicts peak oxygen uptake and survival in patients with advanced heart failure. *Chest* 1996; 110: 325 – 32

Carvalho VO, Bocchi EA and Guimarães GV. The Borg scale as an important tool of self-monitoring and self-regulation of exercise prescription in heart failure patients during hydrotherapy. A randomized blinded controlled trial. *Circulation Journal* 2009; 73; 1871 – 1876

Carvalho VO and Mezzani A. Aerobic exercise training intensity in patients with chronic heart failure: principles of assessment and prescription. *European Journal of Cardiovascular Prevention and Rehabilitation* 2011; 18(1): 5 – 14

Chen YM, Li ZB, Zhu M and Cao M. Effects of exercise training on left ventricular remodelling in heart failure patients: an updated meta-analysis of randomised controlled trials. *International Journal of Clinical Practice* 2012; 66(8): 782 – 791

Clark AL and Coats AJS. Chronotropic incompetence in chronic heart failure. *International Journal of Cardiology*; 1995; 49(3): 225 – 231

Clerico A, Lervasi G, Del Chicca MG, Emdin M, Maffei S, Nannipieri M, Sabatino L, Forini F, Manfredi C and Donato L. Circulating levels of cardiac natriuretic peptides (ANP and BNP) measured by highly sensitive and specific

immunoradiometric assays in normal subjects and in patients with different degrees of heart failure. *Journal of Endocrinological Investigation* 1998; 21(3): 170 – 179

Cohen L, Holliday M. Practical statistics for students: an introductory text. Paul Chapman Publishing, London. 1996

Conraads VM, Beckers P, Vaes J, Martin M, Van Hoof V, de Maeyer C, Possemiers N, Wuyts FL and Vrints CJ. Combined endurance/resistance training reduces NT-proBNP levels in patients with chronic heart failure. *European Heart Journal* 2004; 25: 1797 – 1805

Conraads VM, Vanderheyden M, Paelinck B, Verstreken S, Blankoff I, Miljoen H, De Sutter J and Beckers P . The effect of endurance training on exercise capacity following cardiac resynchronization therapy in chronic heart failure patients; a pilot trial. *European Journal of Cardiovascular Prevention and Rehabilitation* 2007; 14: 99 – 106

Corvera-Tindel T, Doering LV, Woo MA, Khan S and Dracup K. Effects of a home walking exercise program on functional status and symptoms in heart failure. *American Heart Journal* 2004; 147(2): 339 – 346

Cowie MR, Collinson PO, Dargie H, Hobbs R, McDonagh TA, McDonald K and Rowell N. Recommendations on the clinical use of B-type natriuretic peptide testing (BNP or NTproBNP) in the UK and Ireland. *British Journal of Cardiology* 2010; 17:76 – 80

Cowie MR, Jourdin P, Maisel A, Dahlstrom U, Follath F, Isnard R, Luchner A, McDonagh T, Mair J, Nieminen M and Francis G. Clinical applications of B-type natriuretic peptide (BNP) testing. *European Heart Journal* 2003; 24(19): 1710 – 1718

Cowie MR, Struthers AD, Wood DA, Coats AJ, Thompson SG, Poole-Wilson PA and Sutton GC. Value of natriuretic peptides in assessment of patients with possible heart failure in primary care. *Lancet* 1997; 350(9088): 1349

Criteria Committee, NYHA. Diseases of the heart and blood vessels: Nomenclature and criteria for diagnosis, 6th ed. 1964. Little Brown, and Co., NY.

Davidson PM, Cockburn J, Newton PJ, Webster JK, Betihavas V, Howes L, and Owensby DO. Can a heart failure-specific cardiac rehabilitation program decrease hospitalizations and improve outcomes in high-risk patients? *European Journal of Cardiovascular Prevention and Rehabilitation* 2010; 17: 393 – 402

Davies EJ, Moxham T, Rees K, Singh S, Coats AJS, Ebrahim S, Lough F, Taylor RS. Exercise based rehabilitation for heart failure (review). *Cochrane Database of Systematic Reviews* 2010, Issue 4

Davis ME, Richards AM, Nicholls G, Yandle TG, Frampton CM and Troughton RW. Introduction of metoprolol increases plasma B-type cardiac natriuretic peptides in mild, stable heart failure. *Circulation* 2006; 113: 977 – 985

Debigaré R, Maltais F, Mallet M, Casaburi R and LeBlanc P. Influence of work rate incremental rate on the exercise responses in patients with COPD. *Medicine and Science in Sports and Exercise* 2000; 32(8): 1365 – 1368

De Camargo AA, Justino T, De Andrade CH, Malaguti C, Dal Corso S. Chester step test in patients with COPD: reliability and correlation with pulmonary function test results. *Respiratory Care* 2011; 56(7): 995 – 1001

Demers C, McKelvie RS, Negassa A and Yusuf S, for the RESOLVD Pilot Study Investigators. Reliability, validity and responsiveness of the 6-min walk test in patients with heart failure. *American Heart Journal* 2001; 142: 698 – 703

Department of Health National Service Framework for Coronary Heart Disease 2000

Dickstein K, Cohen-Solal A, Filippatos G, McMurray JJV, Ponikowski P, Poole-Wilson PA, Strömberg A, van Veldhuisen DJ, Atar D, Hoes AW, Keren A, Mebazaa A, Nieminen M, Priori SG and Swedberg K. European Society of Cardiology. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2008. The task force for the diagnosis and treatment of acute and chronic heart failure 2008 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC and endorsed by the European Society of Intensive Care Medicine (ESICM). *European Heart Journal* 2008; 29: 2388 – 2442

Doust JA, Pietrzak E, Dobson A and Glasziou P. How well does B-type natriuretic peptide predict death and cardiac events in patients with heart failure: systematic review. *British Medical Journal* 2005; 330: 625 – 633

Dracup K, Evangelista LS, Hamilton MA, Erikson V, Hage A, Moriguchi J, Canary C, MacLellen WR and Fonarow GC. Effects of a home-based program on clinical outcomes in heart failure. *American Heart Journal* 2007; 154(5): 877 – 883

Enright PL. The six-minute walk test. *Respiratory Care* 2003; 48(8): 783 – 785
Eston RG and Connolly D. The use of ratings of perceived exertion for exercise prescription in patients receiving beta-blocker therapy. *Sports Medicine* 1996; 21(3): 176 – 190

Eston RG, Thompson M (1997) Use of ratings of perceived exertion for predicting maximal work rate and prescribing exercise intensity in patients taking atenolol. *British Journal of Sports Medicine* 1997; 31:114 – 119

Faggiano P, D'Aloia A, Gualeni A, Brentana L, Dei Cas L. The 6 minute walking test in chronic heart failure: indications, interpretation and limitations from a review of the literature. *European Journal of Heart Failure* 2004; 6: 687 – 691

Faggiano P, D'Aloia A, Gualeni A, Lavatelli A and Giordano A. Assessment of oxygen uptake during the six-minute walk test in patients with heart failure: preliminary experience with a portable device. *American Heart Journal* 1997; 134: 203 – 206

Faulkner J and Eston R. Overall and peripheral ratings of perceived exertion during a graded exercise test to volitional exhaustion in individuals of high and low fitness. *European Journal of Applied Physiology* 2007; 101(5): 613 – 620

Flynn KE, Piña IL, Whellan DJ, Lin L, Blumenthal JA, Ellis SJ, Fine LJ, Howlett JG, Keteyian SJ, Kitzman DW, Kraus WE, Houston Miller N, Schulman KA, Spertus JA, O'Connor CM and Weinfurt KP. Effects of exercise training on health status in patients with chronic heart failure: findings from the HF-ACTION randomized controlled trial. *Journal of the American Medical Association* 2009; 301(14): 1451 – 1459

Fraga R, Franco FG, Roveda F, de Matos LNJ, Braga AMFW, Rondon MUPB, Rotta DR, Brum PC, Barretto ACP, Middlekauff HR and Negrão CE. Exercise training reduces sympathetic nerve activity in heart failure patients treated with carvedilol. *European Journal of Heart Failure* 2007; 9: 630 – 636

Franklin SS, Khan SA, Wong ND, Larson MG, Levy D. Is pulse pressure useful in predicting risk factors for coronary heart disease? The Framingham Heart Study. *Circulation* 1999; 100: 354 – 360

Friedl W, Mair J, Thomas S, Pichler M and Puschendorf B. Relationship between natriuretic peptides and hemodynamics in patients with heart failure at rest and after ergometric exercise. *Clinica Chimica Acta*. 1999; 281(1-2): 121 – 126

Gademan MGJ, Swenne CA, Verwey HF, Van der Laarse A, Maan AC, Van de Vooren H, Van Pelt J, Van Exel HJ, Lucas CMHB, Cleuren GVV, Somer S, Schalij MJ and Van der Wall EE. Effect of exercise training on autonomic

derangement and neurohumoral activation in chronic heart failure. *Journal of Cardiac Failure* 2007; 13: 294 – 303

Gary RA, Dunbar SB, Higgins MK, Musselman DL and Smith AL. Combined exercise and cognitive behavioural therapy improves outcomes in patients with heart failure. *Journal of Psychosomatic Research* 2010; 69: 119 – 131

Gary RA, Sueta CA, Dougherty M, Rosenberg B, Cheek D, Preisser J, Neelon V and McMurray R. Home-based exercise improves functional performance and quality of life in women with diastolic heart failure. *Heart and Lung* 2004; 33(4): 210 – 218

Giallauria F, Cirillo P, Lucci R, Pacileo M, De Lorenzo A, D'Agostino M, Moschella S, Psaroudaki M, Del Forno D, Orio F, Vitale DF, Chiariello M and Vigorito C. Left ventricular remodelling in patients with moderate systolic dysfunction after myocardial infarction: favourable effects of exercise training and predictive role of N-terminal pro-brain natriuretic peptide. *European Journal of Cardiovascular Prevention and Rehabilitation* 2008; 15: 113 – 118

Giallauria F, De Lorenzo A, Pilerici F, Manakos A, Lucci R, Psaroudaki M, D'Agostino M, Del Forno D and Vigorito C. reduction of N terminal-pro-brain (B-type) natriuretic peptide levels with exercise-based cardiac rehabilitation in patients with left ventricular dysfunction after myocardial infarction. *European Journal of Cardiovascular Prevention and Rehabilitation* 2006; 13: 625 – 632

Giannuzzi P, Tavazzi L (Chairmen), Study Group Members: Meyer K, Perk J, Drexler H, Dubach P, Myers J, Opasich C and Meyers J. Recommendations for exercise training in chronic heart failure patients. Working Group on Cardiac Rehabilitation & Exercise Physiology and Working Group on Heart Failure of the European Society of Cardiology. *European Heart Journal* 2001; 22: 125 – 135

Giannuzzi P, Temporelli PL, Corrà U and tavazzi L for the ELVD-CHF Study Group. Antiremodeling effect of long-term exercise training in patients with

stable chronic heart failure. Results of the exercise in left ventricular dysfunction and chronic heart failure (ELVD-CHF) trial. *Circulation* 2003; 108: 554 – 559

Gopal M, Karnath B. Clinical diagnosis of heart failure. *Hospital Physician* 2009: 9 – 15

Gottlieb SS, Fisher ML, Freudenberger R, Robinson S, Zietowski G, Alves L, Krichten C, Vaitkevicius P and McCarter R. Effects of exercise training on peak performance and quality of life in congestive heart failure patients. *Journal of Cardiac Failure* 1999; 5(3): 188 – 194

Green D, Watts K, Rankin S, Wong P and O'Driscoll J. A comparison of the shuttle and 6 minute walking tests with measured peak oxygen consumption in patients with heart failure. *Journal of Science in Medicine and Sport* 2001; 4(3): 292 – 300

Guazzi M, Dickstein K, Vicenzi M and Arena R. 6 minute walk test and cardiopulmonary exercise testing in Chronic Heart Failure: a comparative analysis on clinical and prognostic insights. *Circulation: Heart Failure* 2009; 2(6): 549 – 555

Guimarães GV, Carvalho VO and Bocchi EA. Reproducibility of the self-controlled six-minute walking test in heart failure patients. *Clinics* 2008; 63(2): 201 – 206

Guyatt GH, Sullivan MJ, Thompson PJ, Fallen EL, Pugsley SO, Taylor DW and Berman LB. The 6 minute walk: a new measure of exercise capacity in patients with chronic heart failure. *Canadian Medical Association Journal* 1985; 132: 919 – 923

Hambrecht R, Gielen S, Linke A, Fiehn E, Yu J, Walther C, Schoene N and Schuler G. Effects of exercise training on left ventricular function and peripheral resistance in patients with chronic heart failure. A randomized trial. *The Journal of the American Medical association* 2000; 283(23): 3095 – 3101

Haass M, Zugck C and Kübler W. The 6 minute walking test: a cost-effective alternative to spiro-ergometry in patients with chronic heart failure? *Zeitschrift für Kardiologie* 2000; 89(2): 72 – 80

Haykowsky MJ, Liang Y, Pechter D, Jones LW, McAlister FA and Clark AM. A meta-analysis of the effect of exercise training on left ventricular remodelling in heart failure patients. *Journal of the American College of Cardiology* 2007; 49: 2329 – 2336

Head A. Exercise metabolism and b-blocker therapy. *Sports Medicine* 1999; 27(2): 81 – 96

Ho KK, Pinsky JL, Kannel WB, Levy D. The epidemiology of heart failure: the Framingham study. *Journal of American College of Cardiology*, 1993; 22(4 Suppl A): 6A – 13A

Holst R, Kaye D, Richardson M, Krum H, Prior D and Aggarwal A. Improved outcomes from a comprehensive management system for heart failure. *European Journal of Heart Failure* 2001; 3(5): 619 – 625

Ingle L, Shelton RJ, Rigby AS, Nabb S, Clark AL and Cleland JGF. The reproducibility and sensitivity of the 6-min walk test in elderly patients with chronic heart failure. *European Heart Journal* 2005; 26: 1742 – 1751

Januzzi JL. Natriuretic peptide testing: A window into the diagnosis and prognosis of heart failure. *Cleveland Clinic Journal of Medicine* 2006; 73(2): 149 – 157

Januzzi JL and Troughton R. Are serial BNP measurements useful in heart failure management?: Serial natriuretic peptide measurements are useful in heart failure management. *Circulation* 2013; 127: 500 – 508

Jensen KT, Carstens J, Ivarsen P and Pedersen EB. A new fast and reliable radioimmunoassay of brain natriuretic peptide in human plasma. Reference

values in healthy subjects and in patients with different diseases. *Scandinavian Journal of Clinical Laboratory Investigations* 1997; 57: 529 – 540

Jiang W, Kuchibhatla M, Cuffe MS, Christopher EJ, Alexander JD, Clary GL, Blazing MA, Gaulden LH, Califf RM, Krishnan RR and O'Connor CM. Prognostic value of anxiety and depression in patients with chronic heart failure. *Circulation* 2004; 110: 3452 – 3456

Johnson J and Siegel D. The use of selected submaximal step tests in predicting change in the maximal oxygen intake of college women. *Journal of Sports Medicine and Physical Fitness* 1981; 21(3): 259 – 264

Jolly K, Taylor RS, Lip GY, Davies M, Davis R, Mant J, Singh S, Greenfield S, Ingram J, Stubley J, Bryan S and Stevens A. A randomized trial of the addition of home-based exercise to specialist heart failure nurse care: the Birmingham Rehabilitation Uptake Maximisation study for patients with congestive heart failure (BRUM-CHF) study. *European Journal of Heart Failure* 2009; 11: 205 – 213

Jónsdóttir S, Andersen KK, Sigurðsson AF and Sigurðsson SB. The effect of physical training in chronic heart failure. *European Journal of Heart Failure* 2006; 8: 97 – 101

Joo KC, Brubaker PH, MacDougall A, Saikin AM, Ross JH, Whaley MH. Exercise prescription using resting heart rate plus 20 or perceived exertion in cardiac rehabilitation. *Journal of Cardiopulmonary Rehabilitation* 2004; 24:178 – 184

Karloh M, Corrêa KS, Martins LQ, Araujo CL, Matte DL and Mayer AF. Chester step test: assessment of functional capacity and magnitude of cardiorespiratory response in patients with COPD and healthy subjects. *Brazilian Journal of Physical Therapy* 2013; 17(3): 227 – 235

Karvonen MJ, Kentala E and Mustala O. The effects of training on heart rate: a longitudinal study. *Annales of Medicinae Experimentalis et Biologiae Fenniae* 1957; 35: 307 – 315

Kato M, Kinugawa T, Ogino K, Endo A, Osaki S, Igawa O, Hisatome I and Shigemasa C. Augmented response in plasma brain natriuretic peptide to dynamic exercise in patients with left ventricular dysfunction and congestive heart failure. *Journal of Internal Medicine* 2000; 248: 309 – 315

Kearon MC, Summers E, Jones NL, Campbell EJ and Killian KJ. Effort and dyspnoea during work of varying intensity and duration. *European Respiratory Journal* 1991; 4(8): 917 – 925

Kemps HMC, Schap G, Hoogsteen J, Thijssen EJM, De Vries WR, Zonderland M and Doevendans P. Oxygen uptake kinetics in CHF: clinical and physiological aspects. *Netherlands Heart Journal* 2009; 17(6): 238 – 244

Keteyian SJ, Kitzman D, Zannad F, Landzberg J, Arnold M, Brubaker P, Brawner CA, Bensimhon D, Hellkamp AS and Ewald G. Predicting maximal heart rate in heart failure patients receiving beta-blockade therapy. *Medicine and Science in Sports and Exercise* 2012; 44(3): 371 – 376

Kitzman DW, Brubaker PH, Morgan TM, Stewart KP and Little WC. Exercise training in older patients with heart failure and preserved ejection fraction. *Circulation Heart Failure* 2010; 3(6): 659 – 667

Klecha A, Kawecka-Jaszcz K, Bacior B, Kubinyi A, Pasowicz M Klimeczek P and Banyś R. Physical training in patients with chronic heart failure of ischemic origin: effect on exercise capacity and left ventricular remodeling. *European Journal of Cardiovascular Prevention and Rehabilitation* 2007; 14: 85 – 91

Klocek M, Kubinyi A, Bacior B and Kawecka-Jaszcz K. Effect of physical training on quality of life and oxygen consumption in patients with congestive heart failure. *International Journal of Cardiology* 2005; 103: 323 – 329

Kociol RD, Pang PS, Gheorghiade M, Fonarow GC, O'Connor CM and Felker GM. Troponin elevation in heart failure. *Journal of the American College of Cardiology* 2010; 56: 1071 – 1078

Koglin J, Pehlivanli S, Schwaiblmair M, Vogeser M, Cremer P and von Scheidt W. Role of brain natriuretic peptide in risk stratification of patients with heart failure. *Journal of the American College of Cardiology* 2001; 38(7): 1934 – 1941

Kosak M and Smith T. Comparison of the 2-, 6- and 12-minute walk tests in patients with stroke. *Journal of Rehabilitation Research and Development* 2005; 42(1): 103 – 108

Koukouvou G, Kouidi E, Iacovides A, Konstantinidou E, Kaprinis G and Deligiannis A. Quality of life, psychological and physiological changes following exercise training in patients with chronic heart failure. *Journal of Rehabilitation Medicine* 2004; 36: 36 – 41

Kowalchuk JM and Hughson RL. Effect of beta-adrenergic blockade on VO_2 kinetics during pseudorandom binary sequence exercise. *European Journal of Applied Physiology and Occupational Physiology* 1990; 60(5): 365 – 369

Krüger S, Graf J, Merx MW, Stickel T, Kunz D, Hanrath P and Janssens U. Brain natriuretic peptide kinetics during dynamic exercise in patients with chronic heart failure. *International Journal of Cardiology* 2004; 95: 49 – 54

Lainchbury JG and Richards AM. Exercise testing in the assessment of chronic congestive heart failure. *Heart* 2002; 88: 538 – 543

Lainchbury JG, Swanney MP, Beckert L, Troughton RW, Yandle TG, Nicholls MG and Richards AM. Change in plasma BNP during exercise is an important predictor of survival in systolic heart failure. *European Heart Journal* 2001; 22(supplement): 377

Lamb KL, Eston RG and Corns D. Reliability of ratings of perceived exertion during progressive treadmill exercise. *British Journal of Sports Medicine* 1999; 33: 336 – 339

Latin RW, Berg K, Kissinger K, Sinnott A and Parks L. The accuracy of the ACSM stair-stepping equation. *Medicine and Science in Sports and Exercise* 2001; 10: 1785 – 1787

Leslie R. Clinical usefulness of B-type natriuretic peptide in cardiac rehabilitation and heart failure. *British Journal of Cardiac Nursing* 2010; 5(10): 472 – 476

Leslie R and Buckley JP. The clinical effectiveness of exercise training for patients with chronic heart failure. *British Journal of Cardiac Nursing* 2010; 5(3): 133 – 139

Leslie R and Buckley JP. Low pulse pressure does not reduce the efficacy of a heart failure exercise programme. *British Journal of Cardiology* 2012; 19:30 – 33

Leung ASY, Chan KK, Sykes K and Chan KS. Reliability, validity and responsiveness of a 2-minute walk test to assess exercise capacity of COPD patients. *Chest* 2006; 130: 119 – 125

Lipkin D, Scriven AJ, Crake T and Poole-Wilson PA. Six minute walking test for assessing exercise capacity in chronic heart failure. *British Medical Journal* 1986; 292: 653 – 655

Lloyd-Williams F, Mair FS and Leitner M. Exercise training and heart failure: a systematic review of current evidence. *British Journal of General Practice* 2002; 52: 47 – 55

Lucas C, Stevenson LW, Johnson W, Hartley H, Hamilton MA, Walden J, Lem V and Eagen-Bengsten E. The 6-min walk and peak oxygen consumption in

advanced heart failure: aerobic capacity and survival. *American Heart Journal* 1999; 138: 618 – 624

McAlister F, Ezekowitz J, Wiebe N, Rowe B, Spooner C, Crumley E. Cardiac resynchronization therapy for congestive heart failure. *Evidence Report/Technology Assessment (Summary)* 2004; 106: 1 – 8

McCullough PA. B-type natriuretic peptide and its clinical implications in heart failure. *American Heart Hospital Journal* 2004; 2: 26 – 33

McKelvie RS, Teo KK, Roberts R, McCartney N, Humen D, Montague T, Hendrican K and Yusuf S. Effects of exercise training in patients with heart failure: the Exercise Rehabilitation Trial (EXERT). *American Heart Journal* 2002; 144: 23 – 30

McMurray JJV, Adamopoulos S, Anker SD, Auricchio A, Böhm M, Dickstein K, Falk V, Filippatos G, Fonseca C, Gomez-Sanchez MA, Jaarsma T, Køber L, Lip GYH, Maggioni AP, Parkhomenko A, Pieske BM, Popescu BA, Rønnevik PK, Rutten FH, Schwitter J, Seferovic P, Stepinska J, Trindade PT, Voors AA, Zannad F and Zeiher A. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012. The task force for the diagnosis and treatment of acute and chronic heart failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. *European Heart Journal* 2012; 33: 1787 – 1847

McNairy M, Gardetto N, Clopton P, Garcia A, Krishnaswamy P, Kazanegra R, Ziegler M and Maisel AS. Stability of B-type natriuretic peptide levels during exercise in patients with congestive heart failure: implications for outpatient monitoring with B-type natriuretic peptide. *American Heart Journal* 2002; 143(3): 406 – 411

Malfatto G, Branzi G, Osculati G, Valli P, Cuoccio P, Ciambellotti F, Parati G and Facchini M. Improvement in left ventricular diastolic stiffness induced by

physical training in patients with dilated cardiomyopathy. *Journal of Cardiac Failure* 2009; 15(4): 327 – 333

Mandic S, Tymchak W, Kim D, Daub B, Quinney HA, Taylor D, Al-Kurtass S and Haykowsky MJ. Effects of aerobic or aerobic and resistance training on cardiorespiratory and skeletal muscle function in heart failure: a randomized controlled pilot trial. *Clinical Rehabilitation* 2009; 23: 207 – 216

Mandic S, Walker R, Stevens E, Nye ER, Body D, Barclay L and Williams MJ. Estimating exercise capacity from walking tests in elderly individuals with stable coronary artery disease. *Disability and Rehabilitation* 2013; 35(22): 1853 – 1858

Mangiafico S, Costello-Boerrigter LC, Anderson IA, Cataliotti A and Burnett Jr JC. Neutral endopeptidase inhibition and the natriuretic peptide system: an evolving strategy in cardiovascular therapeutics. *European Heart Journal* 2013; 34: 886 – 893

Matsumoto A, Hirata Y, Momomura S, Suzuki E, Yokoyama I, Sata M, Ohtani Y, Serizawa T. Effects of exercise on plasma level of brain natriuretic peptide in congestive heart failure with and without left ventricular dysfunction. *American Heart Journal* 1995; 129(1): 139 – 145

Members of the council of the British Association for Cardiac Prevention and Rehabilitation. RAMIT presents an out-dated version of cardiac rehabilitation. *Heart* 2012; 98: 672

Meyer T, Schwaab B, Gorge G, Scharhag J, Herrmann M and Kindermann W. Can serum NT-proBNP detect changes of functional capacity in patients with chronic heart failure? *Zeitschrift fur Kardiologie* 2004; 93: 540 – 545

Miller WL, Phelps MA, Wood CM, Schellenberger U, Van Le A, Perichon R and Jaffe AS. Comparison of mass spectrometry and clinical assay measurements of circulating fragments of B-type natriuretic peptide in patients with chronic heart failure. *Circulation Heart Failure* 2011; 4:355 – 360

Montes J, McDermott MP, Martens WB, Dunaway S, Glanzman AM, Riley S, Quigley J, Montgomery MJ, Sproule D, Tawil R, Chung WK, Darras BT, DeVivo DC, Kaufmann P and Finkel RS. Six-minute walk test demonstrates motor fatigue in spinal muscular atrophy. *Neurology* 2010; 74: 833 – 838

Morales FJ, Martínez A, Méndez M, Agarrado a, Ortega F, Fernández-Guerra J, Montmayor T and Burgos J. A shuttle walk test for assessment of functional capacity in chronic heart failure. *American Heart Journal* 1999; 138(2): 292 – 297

Mottram PM, Haluska BA and Marwick TH. Response of B-type natriuretic peptide to exercise in hypertensive patients with suspected diastolic heart failure: correlation with cardiac function, hemodynamics, and workload. *American Heart Journal* 2004; 148: 365 – 370

Myers J, Wagner D, Schertler T, Beer M, Luchinger R, Klein M, Rickli H, Muller P, Mayer K, Schwitter J and Dubach P. Effects of exercise training on left ventricular volumes and function in patients with nonischemic cardiomyopathy: application of magnetic resonance myocardial tagging. *American Heart Journal* 2002; 144: 719 – 725

Myers J, Zaheer N, Quaglietti S, Madhaven R, Froelicher V and Heidenreich P. Association of functional and health status measures in heart failure. *Journal of Cardiac Failure* 2006; 12(6): 439 – 445

National Audit for Cardiac Rehabilitation Annual Statistical Report 2013, British Heart Foundation 2013

National Clinical Guidelines Centre for Acute and Chronic Conditions (2010) *Chronic Heart Failure: National Clinical Guideline for Diagnosis and Management in Primary and Secondary Care*. August [Full version of NICE CG108] <http://www.nice.org.uk/CG108>

Ni H, Toy W, Burgess D, Wise K, Nauman DJ, Crispell K, Hershberger RE. Comparative responsiveness of short-form 12 and Minnesota living with heart failure questionnaire in patients with heart failure. *Journal of Cardiac Failure*, 2000; 6: 83 – 91

Nilsson BB, Westheim A, Risberg MA, Arnesen H and Seljeflot I. no effect of group-based aerobic interval training on N-terminal pro-B-type natriuretic peptide levels in patients with chronic heart failure. *Scandinavian Cardiovascular Journal* 2010; 44: 223 – 229

Normandin E, Nigam A, Meyer P, Juneau P, Guiraud T, Bosquet L, Mansour A and Gayda M. Responses to Intermittent and Continuous Exercise in Heart Failure Patients. *The Canadian Journal of Cardiology* 2013; 29(4): 466 – 471

O'Connor CM, Whellan DJ, Lee KL, Keteyian SJ, Cooper LS, Ellis SJ, Leifer ES, Kraus WE, Kitzman DW, Blumenthal JA, Rendall DS, Houston Miller N, Fleg JL, Schulman KA, McKelvie RS, Zannad F and Piña IL for the HF-ACTION Investigators. Efficacy and safety of exercise training inpatients with chronic heart failure: HF-ACTION randomized controlled trial. *The Journal of the American Medical Association* 2009; 301(14): 1439 – 1450

O'Keeffe ST, Lye M, Donnellan C and Carmichael DN. Reproducibility and responsiveness of quality of life assessment and six minute walk test in elderly heart failure patients. *Heart* 1998; 80: 377 – 382

Olsson LG, Swedberg K, Cleland JGF, Spark PA, Omajda MK, Metra M, Torp-Pedersen C, Remme WJ, Scherhag A and Poole-Wilson P. Prognostic importance of plasma NT-pro BNP in chronic heart failure in patients treated with a β -blocker: Results from the Carvedilol Or Metoprolol European Trial (COMET) trial *European Journal of Heart Failure* 2007; 9(8): 795 – 801

Opasich C, Pinna GD, Mazza A, Febo O, Riccardi PG, Capomolla S, Cobelli F and Tavazzi L. Reproducibility of the 6-min walking test in patients with chronic congestive heart failure. *American Journal of Cardiology* 1998; 81: 1497 – 500

Opasich C, Pinna GD, Mazza A, Febo O, Riccardi R, Riccardi PG, Capomolla S, Forni G, Cobelli F and Tavazzi L. Six-minute walking performance in patients with moderate-to-severe heart failure; is it a useful indicator in clinical practice? *European Heart Journal* 2001; 22: 488 – 496

Owen A and Croucher L. Effect of an exercise programme for elderly patients with heart failure. *European Journal of Heart Failure* 2000; 2: 65 – 70

Palevo G, Keteyian SJ, Kang M and Caputo JL. Resistance exercise training improves heart function and physical fitness in stable patients with heart failure. *Journal of Cardiopulmonary Rehabilitation and Prevention* 2009; 29: 294 – 298

Parker K, Stone JA, Arena R, Lundberg D, Aggarwal S, Goodhart D and Traboulsi M. An early cardiac access clinic significantly improves cardiac rehabilitation participation and completion rates in low-risk ST-elevation myocardial infarction patients. *Canadian Journal of Cardiology* 2011; 27(5): 619 – 627

Parnell MM, Holst DP and Kaye DM. Exercise training increases arterial compliance in patients with congestive heart failure. *Clinical Science* 2002; 102(1): 1 – 7

Passino C, Severino S, Poletti R, Piepoli MF, Mammini C, Clerico A, Gabutti N, Nassi G and Emdin M. Aerobic training decreases B-type natriuretic peptide expression and adrenergic activation in patients with heart failure. *Journal of the American College of Cardiology* 2006; 47(9): 1835 – 1839

Passino C, Del Ry S, Severino S, Gabutti A, Prontera C, Clerico A, Giannessi D and Emdin M. C-type natriuretic peptide expression in patients with chronic heart failure: effects of aerobic training. *European Journal of Cardiovascular Prevention and Rehabilitation*. 2008; 15: 168 – 172

Peacock IV WF. The B-type natriuretic peptide assay: a rapid test for heart failure. *Cleveland Clinic Journal of Medicine* 2002; 69(3): 243 – 251

Petrie CJ, Robertson M, Voors AA, van Veldhuisen DJ, Dargie HJ. A low pulse pressure predicts mortality in patients with left ventricular dysfunction post myocardial infarction, but only in those with signs and symptoms of heart failure. *Circulation* 2007; 116: II_579

Piepoli MF, Conraads V, Corrà U, Dickstein K, Francis DP, Jaarsma T, McMurray J, Pieske B, Piotrowicz E, Schmid JP, Anker SD, Cohen Solal A, Filippatos GS, Hoes AW, Gielen S, Giannuzzi P and Ponikowski PP. Exercise training in heart failure: from theory to practice. A consensus document of the Heart Failure Association and the European Association for Cardiovascular Prevention and Rehabilitation. *European Journal of Heart Failure* 2011; 13: 347 – 357

Pieske B. Reverse remodeling in heart failure – fact or fiction? *European Heart Journal Supplements* 2004; 6 (supplement D): D66 – D78

Piña IL, Apstein CS, Balady GJ, Belardinelli R, Chaitman BR, Duscha BD, Fletcher BJ, Fleg JL, Meyers JN and Sullivan MJ. Exercise and heart failure: a statement from the American Heart Association Committee on Exercise, Rehabilitation and Prevention. *Circulation* 2003; 107: 1210 – 1225

Pollentier B, Irons SL, Benedetto CM, DiBenedetto AM, Loton D, Seyler RD, Tych M and Newton RA. Examination of the six minute walk test to determine functional capacity in people with Chronic Heart Failure: a systematic review. *Cardiopulmonary Physical Therapy Journal* 2010; 21(1): 13 – 21

Powell LH, Catellier D, Freedland KE, Burg MM, Woods SL, Bittner V, Calvin JE and Blumenthal JA for the ENRICHD Investigators. Depression and heart failure in patients with a new myocardial infarction. *American Heart Journal* 2005; 149(5): 851 – 855

Pu CT, Johnson MT, Forman DE, Hausdorff JM, Roubenoff R, Foldvari M, Fielding RA and Singh MA. Randomized trial of progressive resistance training to counteract the myopathy of chronic heart failure. *Journal of Applied Physiology* 2001; 90: 2341 – 2350

Pulz C, Diniz R, Alves A Incremental shuttle and six-minute walking tests in the assessment of functional capacity in chronic heart failure. *Canadian Journal of Cardiology* 2008; 24(2): 131 – 135

Rector T, Kubo S and Cohn J. Patient self-assessment of their heart failure. Part 2. Content, reliability and validity of a new measure, the Minnesota Living with Heart Failure questionnaire. *Heart Failure* 1987; Oct/Nov: 198 – 209

Redelmeier DA, Bayoumi AM, Goldstein RS and Guyatt GH. Interpreting small differences in functional status: the six minute walk test in chronic lung disease patients. *American Journal of Respiratory Care Medicine* 1997; 155: 1278 – 1282

Rees K, Taylor RS, Singh S, Coats AJS and Ebrahim S. Exercise based rehabilitation for heart failure. *Cochrane Database of Systematic Reviews* 2004, Issue 3

Rengo G, Pagano G, Parisi V, Femminella GD, de Lucia C, Liccardo D, Cannavo A, Zincarelli C, Komici K, Paolillo S, Fusco F, Koch WJ, Filardi PP, Ferrara N and Leosco D. Changes of plasma norepinephrine and serum N-terminal pro-brain natriuretic peptide after exercise training predict survival in patients with heart failure. *International Journal of Cardiology* 2014; 171: 384 – 389

Richards M, Nicholls MG, Espiner EA, Lainchbury JG, Troughton RW, Elliott J, Frampton CM, Crozier IG, Yandle TG, Doughty R, MacMahon S and Sharpe N. Comparison of B-type natriuretic peptides for assessment of cardiac function and prognosis in stable ischaemic heart disease. *Journal of the American College of Cardiology* 2006; 47: 52 – 60

Riley M, McParland J, Stanford CF and Nicholls DP. Oxygen consumption during corridor walk testing in chronic cardiac failure. *European Heart Journal* 1992; 13: 789 – 793

Robergs RA and Landwehr R. The surprising history of the “HRmax=220-age” equation. *Journal of Exercise Physiology online* 2002; 5(2): 1 – 10

Roberts E, Li FKW and Sykes K. Validity of the 6-minute walk test for assessing heart rate recovery after an exercise-based cardiac rehabilitation programme. *Physiotherapy* 2006; 92(2): 116 – 121

Rossier P and Wade DT. Validity and reliability comparison of 4 mobility measures in patients presenting with neurologic impairment. *Archives of Physical Medicine and Rehabilitation* 2001; 82(1): 9 – 13

Rostagno C and Gensini GF. Six minute walk test: a simple and useful test to evaluate functional capacity in patients with heart failure. *Internal and Emergency Medicine* 2008; 3(3): 205 – 212

Rostagno C, Olivo G, Comeglio M, Boddi V, Banchelli M, Galanti G and Gensini GF. Prognostic value of 6-minute walk corridor test in patients with mild to moderate heart failure: comparison with other methods of functional evaluation. *European journal of Heart Failure* 2003; 5: 247 – 252

Roul G, Germain P and Bareiss P. Does the 6-min walk test predict the prognosis in patients with NYHA class II or III chronic heart failure? *American Heart Journal* 1998; 136: 449 – 457

Rutledge T, Reis VA, Linke SE, Greenberg BH and Mills PJ. Depression in heart failure. *Journal of the American College of Cardiology* 2006; 48(8): 1527 – 1537

Sakurai S, Adachi H, Hasegawa A, Hoshizaki H, Oshima S, Taniguchi K and Kurabayashi M. Brain natriuretic peptide facilitates severity classification of

stable chronic heart failure with left ventricular dysfunction. *Heart* 2003; 89: 661 – 662

Sandercock GRH, Cardoso F, Almodhy M and Pepera G. Cardiorespiratory fitness changes in patients receiving comprehensive outpatient cardiac rehabilitation in the UK: a multicentre study. *Heart* 2013; 99(11): 785 – 790

Santos JM, Kowatsch I, Tsutsui JM, Negrão CE, Canavesi N, Frimm CC, Mady C, Ramires JAF and Mathias W. Effects of exercise training on myocardial blood flow reserve in patients with heart failure and left ventricular systolic dysfunction. *American Journal of Cardiology* 2010; 105: 243 – 248

Sarullo FM, Gristina T, Brusca I, Milia S, Raimondi R, Sajeva M, La Chiusa SM, Serio G, Paterna S, Di Pasquale P and Castello A. Effect of physical training on exercise capacity, gas exchange and N-terminal pro-brain natriuretic peptide levels in patients with chronic heart failure. *European Journal of Cardiovascular Prevention and Rehabilitation* 2006; 13: 812 – 817

Scharhag JK, George K, Shave R, Urhausen A and Kindermann W. Exercise-associated increases in cardiac biomarkers. *Medicine and Science in Sports and Exercise* 2008; 40(8): 1408 – 1415

Shave R, George K and Gaze D. The influence of exercise upon cardiac biomarkers: a practical guide for clinicians and scientists. *Current Medicinal Chemistry* 2007; 14: 1427 – 1436

Shelton RJ, Ingle L, Rigby AS, Witte KK, Cleland JGF, Clark AL. Cardiac output does not limit submaximal exercise capacity in patients with chronic heart failure. *European Journal of Heart Failure* 2010; 12(9): 983 – 989

Shoemaker MJ, Curtis AB, Vangsnes E, Dickinson MG. Triangulating clinically meaningful change in the six-minute walk test in individuals with chronic heart

failure: a systematic review. *Cardiopulmonary Physical Therapy Journal* 2012; 23(3); 5 – 15

Skough Vreede K, Henriksson J, Borg K and Henriksson M. Gait characteristics and influence of fatigue during the 6-minute walk test in patients with post-polio syndrome. *Journal of Rehabilitation Medicine* 2013; 45: 924 – 928

Smart N. Exercise training for heart failure patients with and without systolic dysfunction: an evidence-based analysis of how patients benefit. *Cardiology Research and Practice* 2011; (2011): <http://dx.doi.org/10.4061/2011/837238>

Smart NA, Meyer T, Butterfield JA, Faddy SC, Passino C, Malfatto G, Jónsdóttir S, Sarullo F, Wisløff U, Vigorito C and Giallauria F. Individual patient meta-analysis of exercise training effects on systemic brain natriuretic peptide expression in heart failure. *European Journal of Cardiovascular Prevention and Rehabilitation*. 2011; 00(00): 1 – 8

Smart NA and Murison R. Rate of change in physical fitness and quality of life and depression following exercise training in patients with congestive heart failure. *Congestive Heart Failure* 2013; 19(1): 1 – 5

Smart NA and Steele M. Systematic review of the effect of aerobic and resistance exercise training on brain natriuretic peptide (BNP) and N-terminal BNP expression in heart failure patients. *International Journal of Cardiology* 2010; 140: 260 – 265

Spertus J, Peterson E, Conard MW, Heidenreich PA, Krumholz HM, Jones P, McCullough PA, Piña I and Tooley J. Monitoring clinical changes in patients with heart failure: a comparison of methods. *American Heart Journal* 2005; 150(4): 707 – 715

Steele IC, McDowell G, Moore A, Campbell NPS, Shaw C, Buchanan KD and Nicholls DP. Responses of atrial natriuretic peptide and brain natriuretic peptide to exercise in patients with chronic heart failure and normal control subjects. *European Journal of Clinical Investigation* 1997; 27(4): 270 – 276

Stevenson LW, Perloff JK. The limited reliability of physical signs for estimating hemodynamics in chronic heart failure. *Journal of the American Medical Association* 1989; 2 (6): 884 – 888

Sullivan MJ and Hawthorne MH. Exercise intolerance in patients with chronic heart failure. *Progress in Cardiovascular Disease* 1995; 38(1): 1 – 22

Swinburn CR, Wakefield JM and Jones PE. Performance, ventilation, oxygen consumption in three different types of exercise test in patients with chronic obstructive pulmonary disease. *Thorax* 1985; 40(8): 581 – 586

Sykes K. Capacity assessment in the workplace: a new step test. *Journal of Occupational Health* 1995; 1: 20 – 22

Sykes K. Chester step test; resource pack (Version 3). Cheshire, UK; Chester College of Higher Education, 1998. Revised Second Edition 2005

Sykes K and Roberts A. The Chester step test - a simple yet effective tool for the prediction of aerobic capacity, *Physiotherapy* 2004; 90 (4): 183 – 188

Tabet JY, Meurin P, Ben Driss A, Thabut G, Weber H, Renaud N, Odjinkem N and Solal AC. Determination of exercise training heart rate in patients on beta-blockers after myocardial infarction. *European Journal of Cardiovascular and Preventative Rehabilitation* 2006; 13(4): 538 – 543

Tavazzi L, Giannuzzi P (chairmen). Study Group members: Dubach P, Opasich C, Myers J, Perk J, Meyer K and Drexler H. Working Group on Cardiac Rehabilitation and Exercise Physiology and Working group on Heart Failure of the European Society of Cardiology. Recommendations for exercise testing in chronic heart failure patients. *European Heart Journal* 2001; 22: 37 – 45

Taylor RS, Sagar VA, Davies EJ, Briscoe S, Coats AJS, Dalal H, Lough F, Rees K and Singh S. Exercise-based rehabilitation for heart failure (review).

Cochrane Database of Systematic Reviews 2014, Issue 4

The British Association for Cardiovascular Prevention and Rehabilitation
Standards and Core Components for Cardiovascular Disease Prevention and
Rehabilitation 2012 (2nd Edition)

The Criteria Committee of the New York Heart Association. Nomenclature and
criteria for diagnosis of diseases of the heart and great vessels 1994 (9th
Edition), Boston, Massachusetts: Little, Brown & Co

Tiukinhoy SD, Gluckman TJ, Weinberg KM, Jain P, Bello D, Kadish AH and
Goldberger JJ. Autonomic effects on heart rate recovery in patients with
coronary artery disease. *Journal of the American College of Cardiology* 2003;
41(6s1): 167 – 167

Tyni-Lenne R, Dencker K, Gordon A, Jansson E and Sylven C. Comprehensive
local muscle training increases aerobic working capacity and quality of life and
decreases neurohormonal activation in patients with chronic heart failure.
European Journal of Heart Failure 2001; 3: 47 – 52

Tyni-Lenne R, Gordon A, Jansson E, Bermann G and Sylven C. Skeletal
muscle endurance training improves peripheral oxidative capacity, exercise
tolerance and health-related quality of life in women with chronic congestive
heart failure secondary to either ischemic cardiomyopathy or idiopathic dilated
cardiomyopathy. *American Journal of Cardiology* 1997; 80: 1025 – 1029

Tyni-Lenne R, Gordon A and Sylven C. Improved quality of life in chronic heart
failure patients following local endurance training with leg muscles. *Journal of
Cardiac Failure* 1996; 2(2): 111 – 117

Upton CJ, Tyrrell JC and Hiller EJ. Two minute walking distance in cystic
fibrosis. *Archives of Disease in Childhood* 1988; 63: 1444 – 1448

Van den Berg-Emons R, Balk A, Bussmann H and Stam H. Does aerobic training lead to a more active lifestyle and improved quality of life in patients with chronic heart failure? *European journal of Heart Failure* 2004; 6: 95 – 100

van Tol BAF, Huijsmans RJ, Kroon DW, Schothorst M and Kwakkel G. Effects of exercise training on cardiac performance, exercise capacity and quality of life in patients with heart failure: a meta-analysis. *European Journal of Heart Failure* 2006; 8: 841 – 850

Voors AA, Petrie CJ, Petrie MC, Charlesworth A, Hillege HL, Zijlstra F, McMurray JT, van Veldhuisen DJ. Low pulse pressure is independently related to elevated natriuretic peptides and increased mortality in advanced chronic heart failure. *European Heart Journal* 2005; 26: 1759 – 1764

West RR, Jones DA and Henderson AH. Rehabilitation after myocardial infarction (RAMIT): multi-centre randomised controlled trial of comprehensive cardiac rehabilitation in patients following acute myocardial infarction. *Heart* 2012; 98(8): 637 – 644

Wilson JR, Groves J, Rayos G. Circulatory status and response to cardiac in patients with heart failure. *Circulation* 1996; 94: 1567 – 1572

Wisløff U, Støylen A, Loennechen JP, Bruvold M, Rognmo Ø, Haram PM, Tjønnå AE, Helgerud J, Slørdahl SA, Lee SJ, Videm V, Bye A, Smith GL, Najjar SM, Ellingsen Ø and Skjærpe T. Superior cardiovascular effect of aerobic interval training versus moderate continuous training in heart failure patients. A randomized study. *Circulation* 2007; 115: 3086 – 3094

Witham MD, Fulton RL, Greig CA, Johnston DW, Lang CC, van der Pol M, Boyers D, Struthers AD and McMurdo MET. Efficacy and cost of an exercise program for functionally impaired older patients with heart failure: a randomized controlled trial. *Circulation: Heart Failure* 2012; 5: 209 – 216

Witham MD, Gray JM and Argo IS. Effect of a seated exercise program to improve physical function and health status in frail patients > 70 years of age with heart failure. *American Journal of Cardiology* 2005; 95: 1120 – 1124

Wosnich M, Hofmann P, Fruhwald FM, Kraxner W, Hodl R, Pokan R and Klein W. Influence of beta-blocker use on percentage of target heart rate exercise prescription. *European Journal of Cardiovascular Prevention and Rehabilitation* 2003; 10: 296 – 301

Yeh GY, McCarthy EP, Wayne PM, Stevenson LW, Wood MJ, Davis RB and Phillips RS. Tai chi exercise in patients with chronic heart failure: a randomized clinical trial. *Archives of Internal Medicine* 2011; 171: 750 – 757

Yeh GY, Wood MJ, Lorell BH, Stevenson LW, Eisenberg DM, wayne PM, Goldberger AL, Davis RB and Phillips RS. Effects of tai-chi mind-body movement therapy on functional status and exercise capacity in patients with chronic heart failure: a randomized controlled trial. *American Journal of Medicine* 2004; 117: 541 – 548

Yildiran T, Koc M, Bozkurt A, Sahin DY, Unal I and Acarturk E. Low pulse pressure as a predictor of death in patients with mild to advanced heart failure. *Texas Heart Institute Journal* 2010; 37(3): 284 – 290

Zhang YY, Wasserman K, Sietsema KE, Ben-Dor I, Barstow TJ, Mizumoto G and Sullivan CS. Oxygen uptake and kinetics in response to exercise. A measure of tissue anaerobiosis in heart failure. *Chest* 1993; 103(3): 735 – 741

Zigmond A and Snaith R. The Hospital Anxiety and Depression Scale. *Acta Psychiatrica Scandinavica* 1983; 67: 361 – 370

Zugck C, Krüger C, Dürr S, Gerber SH, Haunstetter A, Hornig K, Kübler W and Haass M. Is the 6-minute walk test a reliable substitute for peak oxygen uptake in patients with dilated cardiomyopathy? *European Heart Journal* 2000; 21: 540 – 549

Zwisler AD, Soja AM, Rasmussen S, Frederiksen M, Abedini S, Appel J, Rasmussen H, Gluud C, Iverson L, Sigurd B, Madsen M, Fischer-Hansen J; DANREHAB group. Hospital-based, comprehensive cardiac rehabilitation versus usual care among patients with congestive heart failure, ischemic heart disease or high-risk of ischemic heart disease: 12-month results of a randomized clinical trial. *American Heart Journal* 2008; 155: 1106 – 1113

Appendices

Appendix 1

Rosalind Leslie
Telephone: 01902 694226

Title of Project: The efficacy of exercise therapy for Class II and III Heart Failure Patients

Patient Information Sheet

You are being invited to take part in a research study. Before you decide it is important for you to understand why the research is being done and what it will involve.

Please read the following information carefully and if you have any queries, please discuss them with friends, relatives, hospital doctors or your GP if you wish. Ask me if there is anything that is not clear or if you would like more information.

Who is organising the research study?

This research study is being co-ordinated by Rosalind Leslie, Specialist Physiotherapist in Cardiac Rehabilitation, and will contribute towards an educational qualification (PhD) with Chester University. Rosalind is based in

The Heart and Lung Centre at New Cross Hospital and has extensive clinical experience, having been involved in cardiac rehabilitation for 20 years.

What is the purpose of the study?

The Heart Failure Nurse has referred you to the Heart Failure Exercise Programme. We aim to compare results of a 12-week course of supervised exercise with results after following advice-only to determine the benefit of exercise on your physical and psychological well being, and on the symptoms associated with heart failure.

Do I have to take part?

No. It is up to you to decide whether or not you would like to take part in the study. If you decide to take part you will be given this information sheet to keep and will be asked to sign a consent form. If you do take part, you can stop at any time without giving a reason. A decision to stop at any time, or a decision not to take part, will not affect the standard of care you receive and you can continue to attend the exercise programme.

What will happen if I take part?

If you agree to take part in the study your participation will last for approximately 12 months, which includes the 12-week duration of a course of exercise, a 12-week period where you will be asked to follow advice given by the Heart Failure Nurse and a subsequent 6-month follow-up. The decision as to whether you join the exercise programme first or follow advice first will be taken at random (effectively the toss of a coin – in other words you will not be able to choose which you do first). You will undergo a 30-minute assessment before and after each 12-week period and at a 6-month follow-up. All tests and measurements and the exercise sessions are part of standard care for the Heart Failure Exercise Programme. The blood samples at each assessment will be frozen, stored and then analysed by the Clinical Chemistry Department at New Cross Hospital. There is one heart-specific blood test that is undertaken using these blood samples. By signing the Written Informed Consent Form you are giving permission for this to be done. The results of these assessments will be used in the study. You may, by a process of random selection, be requested to undertake a more in-depth assessment using a piece of equipment that will measure your body's ability to use oxygen. This will involve some discomfort as you will be required to wear a facemask and a heart rate chest strip during the short exercise tolerance test, with a lightweight transmitting unit attached to you with a harness. Information will be transmitted to a computer for analysis. You may, by a process of random selection, be requested to have an echocardiogram. An echocardiogram uses sound waves to build up a detailed picture of your heart and to see how well it is functioning. Lubricating jelly is rubbed on the chest and a probe is then used to produce a pulse of high frequency sound waves which pass through the skin. A picture of your heart can be seen on the screen. A decision not to undertake either of these assessments will not affect your care.

What do I have to do?

You must be willing to follow advice, to complete the Heart Failure Exercise Programme and also attend a maximum of four appointments for assessment.

It is important that you tell the Cardiac Rehabilitation Exercise Specialist or Heart Failure Nurse about all the medicines you take, including those sold over the counter from a chemist shop or supermarket. You must also tell them if you change the dose or stop any medicines.

What are the benefits of taking part in this study?

We hope that attending the exercise programme will improve your fitness and quality of life more so than following advice-only. However, this cannot be guaranteed. The information that we get from this study may help us to provide better treatment to patients with Heart Failure in the future.

What are the possible risks and disadvantages in taking part?

We do not anticipate any untoward effects as a result of taking part in this study. There is no documented evidence to suggest that delaying the start of cardiac rehabilitation exercise training is in any way detrimental to your health.

Will my taking part in this study be kept confidential?

All information that is collected about you during the Exercise Programme will be kept strictly confidential. Data that is required for the research study will be stored and analysed in a computer and will be treated confidentially. If any information about you needs to leave the hospital it will have your name and address removed so that you cannot be recognised from it.

Certain Trust auditors may wish to look at your records to check that the study has been performed correctly. By signing the Written Informed Consent Form you are giving permission for this to be done.

Your confidentiality will be maintained, in accordance with the UK Data Protection Act, 1998, or as local laws permit.

What happens if I suffer as a result of the study?

This is unlikely, but if you wish to complain or have any concerns about any aspect of the way that you were treated during the course of this study, the normal National Health Service complaints mechanism will be available to you.

You do not lose any rights by being in this research.

If you wish to seek some independent advice or have any concerns or complaints, then please contact:

Pauline Boyle, Research Manager
Research & Development Directorate, New Cross Hospital
Telephone Number 01902 695065 or
24 hour contact telephone number: 07776 132837

What will happen to the results of the research study?

The results of the study will be published in about 4 years as it takes time to analyse the results. You will be sent a copy of the results if you wish at that time. You will not be identified in any report/publication.

Who should I contact for further information?

Whenever you want to get more information about this study please contact:
Rosalind Leslie, Clinical Physiotherapist Specialist
Cardiac Rehabilitation Services, Heart and Lung Centre, New Cross Hospital
Telephone number 01902 694226

You can also discuss it with the Patient Advice Liaison Service (PALS), Patient Liaison Centre, New Cross Hospital, Wolverhampton. Telephone number 01902 695362

Thank you for taking the time to read this information.

Parallel study. Version number 2, dated
24/04/09

The Royal Wolverhampton



NHS Trust

Appendix 2

Rosalind Leslie
Telephone: 01902 694226

Title of Project: The efficacy of exercise therapy for Class II and III Heart Failure Patients

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What will happen if I take part?

If you agree to take part in the study your participation will last for approximately 12 months, which includes the 12-week duration of a course of exercise, a 12-week period where you will be asked to follow advice given by the Heart Failure Nurse and a subsequent 6-month follow-up. The decision as to whether you join the exercise programme first or follow advice first will be taken at random (effectively the toss of a coin – in other words you will not be able to choose which you do first).

You will undergo a 30-minute assessment before and after each 12-week period and at a 6-month follow-up. All tests and measurements and the exercise sessions are part of standard care for the Heart Failure Exercise Programme. The blood samples at each assessment will be frozen, stored and then analysed by the Clinical Chemistry Department at New Cross Hospital. There is one heart-specific blood test that is undertaken using these blood samples. By signing the Written Informed Consent Form you are giving permission for this to be done. The results of these assessments will be used in the study. You may, by a process of random selection, be requested to have additional blood tests whilst attending exercise sessions. This will involve one blood test at the end of an exercise session on a Monday and then a daily blood test until your next exercise session on Thursday. This may provide useful information to help determine the ideal frequency of exercise sessions for patients with Heart Failure. You may, by a process of random selection, be requested to undertake a more in-depth assessment using a piece of equipment that will measure your body's ability to use oxygen. This will involve some discomfort as you will be required to wear a facemask and a heart rate chest strip during the short exercise tolerance test, with a lightweight transmitting unit attached to you with a harness. Information will be transmitted to a computer for analysis. You may, by a process of random selection, be requested to have an echocardiogram. An

echocardiogram uses sound waves to build up a detailed picture of your heart and to see how well it is functioning. Lubricating jelly is rubbed on the chest and a probe is then used to produce a pulse of high frequency sound waves which pass through the skin. A picture of your heart can be seen on the screen. A decision not to undertake either of these assessments will not affect your care.

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You must be willing to follow advice, to complete the Heart Failure Exercise Programme and also attend a maximum of four appointments for assessment. It is important that you tell the Cardiac Rehabilitation Exercise Specialist or Heart Failure Nurse about all the medicines you take, including those sold over the counter from a chemist shop or supermarket. You must also tell them if you change the dose or stop any medicines.

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Research & Development Directorate, New Cross Hospital
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Rosalind Leslie, Clinical Physiotherapist Specialist
Cardiac Rehabilitation Services, Heart and Lung Centre, New Cross Hospital
Telephone number 01902 694226

You can also discuss it with the Patient Advice Liaison Service (PALS), Patient Liaison Centre, New Cross Hospital, Wolverhampton. Telephone number 01902 695362

Thank you for taking the time to read this information

Parallel study. Version number 3, dated 29/04/10

Appendix 3

North Staffordshire Local Research Ethics Committee

North Staffordshire Medical Institute
Hartshill Road
Hartshill
Stoke-on-Trent
Staffs
ST4 7NY

Telephone: 01782 714980
Facsimile: 01782 714975

08 June 2009

Mrs Rosalind Leslie
Clinical Physiotherapist Specialist, Cardiac Rehabilitation
Royal Wolverhampton Hospitals
Cardiac Rehabilitation Department
Heart and Lung Centre
New Cross Hospital
WV10 0QP

Dear Mrs Leslie

Study Title: The efficacy of exercise therapy for class II and III heart failure patients
REC reference number: 09/H1204/33
Protocol number: 7

Thank you for your letter of 15 May 2009, responding to the Committee's request for further information on the above research and submitting revised documentation, subject to the conditions specified below.

The further information has been considered on behalf of the Committee by the Chair.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised.

Ethical review of research sites

The favourable opinion applies to all NHS sites taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" below).

Conditions of the favourable opinion

The favourable opinion is subject to the following conditions being met prior to the start of the study.

Management permission or approval must be obtained from each host organisation prior to the start of the study at the site concerned.

For NHS research sites only, management permission for research ("R&D approval") should be obtained from the relevant care organisation(s) in accordance with NHS research

governance arrangements. Guidance on applying for NHS permission for research is available in the Integrated Research Application System or at <http://www.rdforum.nhs.uk>. Where the only involvement of the NHS organisation is as a Participant Identification Centre, management permission for research is not required but the R&D office should be notified of the study. Guidance should be sought from the R&D office where necessary.

Sponsors are not required to notify the Committee of approvals from host organisations.

It is the responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

Document	Version	Date
Physical Activity		11 August 2008
Exercise programme		11 August 2008
CV senior research nurse		11 February 2009
Unfavourable opinion letter		23 April 2008
CV for educational supervisor		02 January 2008
Participant Consent Form	1	11 August 2008
Peer Review		28 January 2009
Summary/Synopsis		11 August 2008
Covering Letter		16 February 2009
Protocol	7	11 August 2008
Investigator CV		11 February 2009
Application		18 February 2009
Response to Request for Further Information		15 May 2009
Participant Information Sheet	2	24 April 2009
Statistician Comments		14 May 2009

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees (July 2001) and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review

Now that you have completed the application process please visit the National Research Ethics Service website > After Review

You are invited to give your view of the service that you have received from the National Research Ethics Service and the application procedure. If you wish to make your views known please use the feedback form available on the website.

The attached document "*After ethical review – guidance for researchers*" gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators

- Progress and safety reports
- Notifying the end of the study

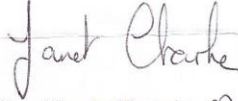
The NRES website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

We would also like to inform you that we consult regularly with stakeholders to improve our service. If you would like to join our Reference Group please email referencegroup@nres.npsa.nhs.uk.

09/H1204/33

Please quote this number on all correspondence

Yours sincerely



Miss Nicola Brooks *pp*
Chair

Email: Janet.Clarke@uhns.nhs.uk

Enclosures:
Copy to:

"After ethical review – guidance for researchers"
Lorraine Evans, Lorraine Evans, R&D Department, New Cross
Hospital, Wolverhampton, WV10 0QP ✓

Appendix 4

The Royal Wolverhampton Hospitals

25 February 2010

NHS Trust

Rosalind Leslie
Clinical Physiotherapist Specialist
Cardiac Rehabilitation
Heart & Lung Centre
New Cross Hospital
Wolverhampton
WV10 0QP

Research & Development Directorate
New Cross Hospital
Wolverhampton
West Midlands
WV10 0QP

Tel: 01902 695065
Fax: 01902 695682

Dear Ms Leslie

Research Project: The efficacy of exercise therapy for class II and III heart failure patients

R&D Project No: 07CARD03

PROTOCOL VERSION: 7 dated 11 Aug 08

The above research project has been reviewed by the Trust through the Research & Development Directorate.

All documents have been received including the approval letter from the main Research Ethics Committee and the Site Specific Information Form for the Trust.

Version of Documents approved:

- Protocol Version 7 dated 11 Aug 08
- Patient Information Sheet Version 2 dated 24 Apr 09
- Consent Form Version 1 dated 11 Aug 08

Due to the nature of the project, Trust Approval is given for the project on the following basis:

1. **Costs and Funding:** The Cardiology Trading account will be utilised to underwrite the outstanding funding requirements, whilst further funding is pursued by yourself. Please provide regular study updates to Dr James Cotton, Consultant Cardiologist.
2. **Research Governance:** All research in the Trust must be conducted within the DoH Research Governance Framework and the Trust's Research Governance and Consent to Clinical Trials policies.
 - a. As part of Research Governance, researchers **must** receive Quality Assurance (QA) training before the study commences, therefore please contact the QA Co-ordinator, Julie Sinclair, in the R&D Directorate on the above telephone number, who will make the decision as to whether QA Training is applicable to your research, and will arrange this if necessary free of charge at a suitable time convenient to the researchers. Alternatively, online GCP training is available from the R&D Directorate. As Chief Investigator, it is your responsibility to ensure that everyone on the research team has received this training.
 - b. Please provide the R&D Directorate with the number of subjects recruited into this study when we contact you on a quarterly basis and also inform us when the study is finished to ensure that the Trust is fully compliant with Research Governance and DoH reporting.

TrustApprovalLetterOwnAccountResearch030807

Page 1 of 2

Chairman: Alan Edwards
Chief Executive: David Loughton

Preventing Infection - Protecting Patients

WCA 820 22.07.08

A Teaching Trust of the University of Birmingham



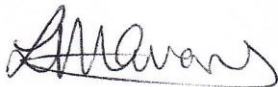
- c. Please notify the Research & Development Directorate of any Serious Adverse Events (SAEs) or SUSARs (Serious Unexpected Suspected Adverse Reactions) within 24 hours of you becoming aware of the event (if applicable), by sending a copy of the report form to the attention of Yvonne Hague, R&D Directorate Manager, Research & Development Directorate.
3. **Amendments:** You are required to submit all amendments to the project, including the changed documents, notification of amendment form and REC approval letter to the R&D Directorate for approval. New versions of documentation can only be used once you have received notification from the R&D Directorate.
4. **Annual Reports:** You are required to submit quarterly reports of progress with this project when requested. The R&D Directorate will send out a template by email for you to complete and return to the Directorate. Continuing Trust Approval is dependent upon providing completed reports and may be withdrawn if you do not complete and return the reports when requested.
5. **Completion of Project:** Please inform the R&D Directorate when your project closes to recruitment and also when the project has finished in order for the files to be archived appropriately and our files to remain up-to-date.
6. **Dissemination of Research Findings:** As with all NHS research, it is expected that the results of this study will be published in a reputable journal, may be presented at various meetings and will influence decisions on best practice. I would be very grateful if you could keep me informed of any publications, presentations and how the results of this research have been implemented into practice. Please note that if this research has been totally or part funded by the NHS, via the Research and Development Directorate, you are required to acknowledge this support on any publications.

Sponsorship: The Research & Development Directorate has agreed to take on the role of Sponsor for your research under the DoH Research Governance Framework for Health & Social Care only if you have returned a signed Delegation of Duties as Chief Investigator Statement that was sent to you upon first notification of project received with the Research & Development Directorate. If you did not receive this to sign please contact me on extension 5065 and I will provide a further copy for you.

On behalf of the Research & Development Directorate, I would like to wish you every success with your research project.

Best wishes

Yours sincerely



Lorraine Evans
Research and Development Project Manager

C.C. Ms Sheila Stringer, Physiotherapy Services,
Ms Kate Middlemiss, Directorate Manager, Cardiology
Mr Alain Rolli, Pathology Services Manager, Clinical Chemistry

Appendix 5



North Staffordshire Research Ethics Committee

Prospect House
Fishing Line Road
Redditch
Worcestershire
B97 6EW

Tel: 01527 582535
Fax:

08 July 2010

Mrs Rosalind Leslie
Clinical Physiotherapist Specialist, Cardiac Rehabilitation
Clinical Physiotherapist Specialist, Cardiac Rehabilitation
Cardiac Rehabilitation Department
Heart and Lung Centre
New Cross Hospital
WV10 0QP

Dear Mrs Leslie

Study title: The efficacy of exercise therapy for class II and III heart failure patients
REC reference: 09/H1204/33
Amendment number: AM01
Amendment date: 12 May 2010

The above amendment was reviewed by the Sub-Committee in correspondence.

Ethical opinion

Favourable Opinion

The members of the Committee taking part in the review gave a favourable ethical opinion of the amendment on the basis described in the notice of amendment form and supporting documentation.

Approved documents

The documents reviewed and approved at the meeting were:

Document	Version	Date
Participant Consent Form	3	29 April 2010
Participant Information Sheet	3	29 April 2010
Protocol	2	29 April 2010
Notice of Substantial Amendment (non-CTIMPs)		12 May 2010

Membership of the Committee

The members of the Committee who took part in the review are listed on the attached sheet.

R&D approval

All investigators and research collaborators in the NHS should notify the R&D office for the relevant NHS care organisation of this amendment and check whether it affects R&D approval of the research.

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees (July 2001) and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

09/H1204/33:

Please quote this number on all correspondence

Yours sincerely



Mrs Jenny Tyers
Committee Co-ordinator

E-mail: jenny.tyers@westmidlands.nhs.uk

Enclosures: List of names and professions of members who took part in the review

Copy to: The Royal Wolverhampton Hospitals NHS Trust
[\[R&D office for NHS care organisation at lead site\]](#)

Appendix 6

The Royal Wolverhampton Hospitals NHS Trust

27 June 2011

Research & Development Directorate

The Chestnuts
Wolverhampton
West Midlands
WV10 0QP

Tel: 01902 695065
Fax: 01902 695682

Rosalind Leslie
Clinical Physiotherapist Specialist
Cardiac Rehabilitation
Heart & Lung Centre
New Cross Hospital
Wolverhampton
WV10 0QP

Dear Ms Leslie

Research Project: The efficacy of exercise therapy for class II and III heart failure patients

R&D Project No: 07CARD03

The above research project has been re-reviewed by the Trust through the Research & Development Directorate in light to the Substantial Amendment 1 dated 12 May 2010.

All documents have been received including the approval letter from the main Research Ethics Committee.

New Version of Documents approved:

- Protocol Version 2 dated 29 Apr 10
- Patient Information Sheet Version 3 dated 29 Apr 10
- Consent Form Version 3 dated 29 Apr 10

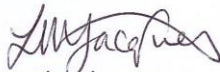
Summary of Amendment (not exhaustive):

1. Additional subgroup of patients will have NT-proBNP levels measured
2. updated study costings and funding

The original Trust approval letter has also been reviewed and the R&D Directorate can confirm that the above substantial amendment has been approved and should be read in conjunction with terms and conditions of the original Trust approval letter.

On behalf of the Research & Development Directorate, I would like to wish you every continued success with your research project.

Best wishes
Yours sincerely



Lorraine Jacques
Research and Development Project Manager

C.C. Ms K Nicholas, Cardiology Department Manager, Heart & Lung Centre
Debra Sylvester, Senior Sister, Cardiac Rehab/OPD, Heart & Lung Centre

Chairman: Barry Picken
Chief Executive: David Loughton CBE
Preventing Infection - Protecting Patients

A Teaching Trust of the University of Birmingham
WCA 820 14.09.10



Appendix 7

CONSENT FORM

Title of Project: The efficacy of exercise therapy for Class II and III Heart Failure Patients

Name of Researcher: Rosalind Leslie, Clinical Physiotherapist Specialist,
Cardiac Rehabilitation Services. Telephone 01902 694226

Patient Identification Number:

Patient
please
initial

1. I confirm that I have read, understood and received a copy of the information sheet version 2 for the above study. ☐
2. The study has been explained to me and I have had the opportunity to ask questions and all my questions have been answered to my satisfaction. ☐
3. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason. ☐
4. I understand that the data collected about me may be looked at by responsible individuals from regulatory authorities of the Trust, where it is relevant to my taking part in research. I give my permission for these individuals to have access to my data. ☐
5. **Consent for storage**

I agree that the blood sample I have given and the information gathered about me can be stored by Rosalind Leslie from Cardiac Rehabilitation, Heart and Lung Centre, New Cross Hospital, for the purpose of this study. ☐
6. I agree to take part in the above study. ☐

Name of Subject Date Signature

Name of Person Date Signature
taking consent

Each individual who signs this document must PERSONALLY date his or her signature. One copy for patient, 1 for researcher.

Appendix 8

CONSENT FORM

Title of Project: The efficacy of exercise therapy for Class II and III Heart Failure Patients

Name of Researcher: Rosalind Leslie, Clinical Physiotherapist Specialist,
Cardiac Rehabilitation Services. Telephone 01902 694226

Patient Identification Number:

Patient
please
initial box

5. I confirm that I have read, understood and received a copy of the information sheet version 3 for the above study. ☐
6. The study has been explained to me and I have had the opportunity to ask questions and all my questions have been answered to my satisfaction. ☐
7. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason. ☐
8. I understand that the data collected about me may be looked at by responsible individuals from regulatory authorities of the Trust, where it is relevant to my taking part in research. I give my permission for these individuals to have access to my data. ☐

5. Consent for storage

I agree that the blood sample I have given and the information gathered about me can be stored by Rosalind Leslie from Cardiac Rehabilitation, Heart and Lung Centre, New Cross Hospital, for the purpose of this study. ☐

6. I agree to take part in the above study. ☐

Name of Subject Date Signature

Name of Person Date Signature
taking consent

Each individual who signs this document must PERSONALLY date his or her signature. One copy for patient, 1 for researcher.

Appendix 9

HAD Scale

Name:

Date:

Doctors are aware that emotions play an important part in most illnesses. If your doctor knows about these feelings he will be able to help you more.

This questionnaire is designed to help your doctor to know how you feel. Read each item and place a firm tick in the box opposite the reply which comes closest to how you have been feeling in the past week.

Don't take too long over your replies: your immediate reaction to each item will probably be more accurate than a long thought-out response.

Tick only one box in each section

I feel tense or 'wound up':

- Most of the time
.....
A lot of the time
.....
Time to time, Occasionally
.....
Not at all
.....

I feel as if I am slowed down:

- Nearly all the time
.....
Very often
.....
Sometimes
.....
Not at all
.....

I still enjoy the things I used to enjoy:

- Definitely as much
.....
Not quite so much
.....
Only a little
.....
Hardly at all
.....

I get a sort of frightened feeling like 'butterflies' in the stomach:

- Not at all
.....
Occasionally
.....
Quite often
.....
Very often
.....

I get a sort of frightened feeling as if something awful is about to happen:

- Very definitely and quite badly
.....
Yes, but not too badly
.....
A little, but it doesn't worry me
.....
Not at all
.....

I have lost interest in my appearance:

- Definitely
.....
I don't take so much care as I should
.....
I may not take quite as much care ..
.....
I take just as much care as ever
.....

I can laugh and see the funny side of things:

- As much as I always could
.....
Not quite so much now
.....
Definitely not so much now
.....
Not at all
.....

I feel restless as if I have to be on the move:

- Very much indeed
.....
Quite a lot ...
.....
Not very much
.....
Not at all
.....

Worrying thoughts go through my mind:

A great deal of the time
.....
A lot of the time
.....
From time to time but not too often .
Only occasionally
.....

I look forward with enjoyment to things:

As much as ever I did
.....
Rather less than I used to
.....
Definitely less than I used to
.....
Hardly at all
.....

I feel cheerful:

Not at all
.....
Not often
.....
Sometimes
.....
Most of the time
.....

I get sudden feelings of panic:

Very often indeed
.....
Quite often ...
.....
Not very often
.....
Not at all
.....

I can sit at ease and feel relaxed:

Definitely
.....
Usually
.....
Not often
.....
Not at all
.....

I can enjoy a good book or radio or TV programme:

Often
.....
Sometimes
.....
Not often
.....
Very seldom
.....

Printed as a service to medicine

Upjohn

Appendix 10

MINNESOTA LIVING WITH HEART FAILURE QUESTIONNAIRE

The following questions ask how much your heart failure (heart condition) affected your life during the past month (4 weeks). After each question, circle the 0, 1, 2, 3, 4 or 5 to show how much your life was affected. If a question does not apply to you, circle the 0 after that question.

Did your heart failure prevent you from living as you wanted during the past month (4 weeks) by –

	No	Very Little				Very Much
1. causing swelling in your ankles or legs?	0	1	2	3	4	5
2. making you sit or lie down to rest during the day?	0	1	2	3	4	5
3. making your walking about or climbing stairs difficult?	0	1	2	3	4	5
4. making your working around the house or yard difficult?	0	1	2	3	4	5
5. making your going places away from home difficult?	0	1	2	3	4	5
6. making your sleeping well at night difficult?	0	1	2	3	4	5
7. making your relating to or doing things with your friends or family difficult?	0	1	2	3	4	5
8. making your working to earn a living difficult?	0	1	2	3	4	5
9. making your recreational pastimes, sports or hobbies difficult?	0	1	2	3	4	5
10. making your sexual activities difficult?	0	1	2	3	4	5
11. making you eat less of the foods you like?	0	1	2	3	4	5
12. making you short of breath?	0	1	2	3	4	5
13. making you tired, fatigued, or low on energy?	0	1	2	3	4	5
14. making you stay in a hospital?	0	1	2	3	4	5
15. costing you money for medical care?	0	1	2	3	4	5
16. giving you side effects from treatments?	0	1	2	3	4	5
17. making you feel you are a burden to your family or friends?	0	1	2	3	4	5
18. making you feel a loss of self-control in your life?	0	1	2	3	4	5
19. making you worry?	0	1	2	3	4	5
20. making it difficult for you to concentrate or remember things?	0	1	2	3	4	5
21. making you feel depressed?	0	1	2	3	4	5

Appendix 11

PHYSICAL ACTIVITY

1 Considering a 7-day period (a week), how many times on average do you do the following kinds of exercise for **more than 15 minutes** (write the appropriate number in the boxes)?

a. Strenuous Activity (heart beats rapidly/tiring)?

(e.g. running, jogging, vigorous long distance cycling, circuit training, aerobic dance, skipping, football, squash, basketball, roller skating, vigorous swimming)

Number of times

b. Moderate Activity (not exhausting)?

(e.g. fast walking, mowing the lawn, tennis, easy cycling, badminton, easy swimming, ballroom dancing, fast or high step ups)

c. Mild Activity (minimal effort)?

(e.g. easy walking, slow dancing, standing active fishing, bowling, golf, low step-ups)

2 Considering a **7-day period** (a week), how often do you engage in any regular activity long enough to work up a sweat (heart beats rapidly)?

Please tick one box

A Often

☐

B Sometimes

☐

C Never/Rarely

☐

3 Do you take regular physical activity of at least 30 minutes duration on average 5 times a week?

Please tick one box

YES

NO

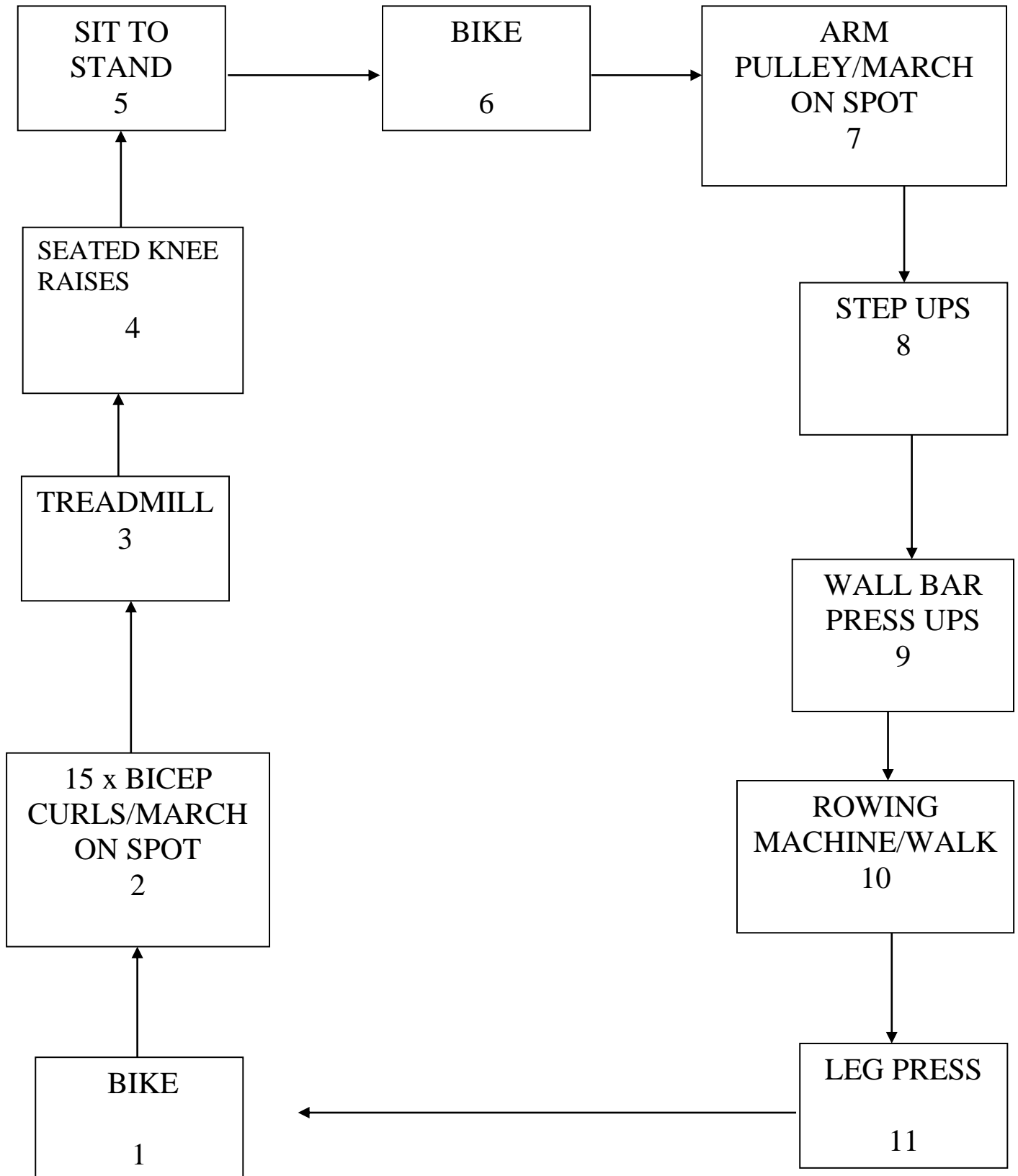
Thank you

Appendix 12

Cardiac Rehabilitation/Heart Failure Exercise Circuit

2 minutes at each exercise station, working at moderate effort.

Speak to the Exercise Specialist if you have difficulty with any of the exercises.



Appendix 13



EFFICACY OF A TWO-MINUTE VERSUS A SIX-MINUTE PRACTICE WALK BEFORE A SIX-MINUTE WALK TEST IN HEART FAILURE PATIENTS

R. Leslie^{1,2}, K. George³, J.P. Buckley²

¹Royal Wolverhampton NHS Trust, UK; ²University of Chester, UK; ³Liverpool John Moore's University, UK

Introduction: The 6-minute walk test (6MWT) is a useful measure of functional capacity for people with moderate to severe cardiorespiratory impairment. Both in clinical practice and in research when using the 6MWT in chronic heart failure (CHF), a practice test is recommended. Current recommendations require patients to perform a full practice test, but there is concern that it may induce fatigue and a 30 min rest before the actual test. A two minute walk test (2MWT) has been reported to be reliable, valid and sensitive in the assessment of patients with moderate to severe COPD (Leung et al, 2006), neurologic impairment (Rossier and Wade, 2001), stroke (Kosak and Smith, 2005) and cardiac surgery (Brooks et al, 2004).

Aims: To assess the efficacy of a 2-minute versus a 6-minute practice test on pacing and possible fatigue during a subsequent 6MWT.

Methods:

- 20 NYHA Class II & III CHF patients (55% from coronary heart disease) recruited:
 - Stable on optimal medical therapy ≥ 4 weeks
 - Symptoms of exertional dyspnoea and/or fatigue
- Group 1 (n = 10; 9 male) performed a 2-minute self-paced practice walk test +20 mins rest, followed by a 6MWT.
- Group 2 (n = 10; 7 male) performed a full 6-minute practice test +20 mins rest, followed by a 6MWT.
- Heart rate (HR) and ratings of perceived exertion (RPE) were monitored throughout all tests.
- A two factor (group by trial) repeated measures ANOVA was used to assess differences in HR and RPE (in the first two minutes) and walking pace (m.min⁻¹) throughout all tests.
- Effects of pacing or fatigue on walking pace were further assessed between practice and follow-up 6MWT using a bias +/- 95% limits of agreement (LoA) analysis.

Results:

- Mean (SD) walking distances and paces in Table 1.
- Within group walking pace was the same for practice and 6MWT (p < .12)
- Although walking paces were different between groups (p = .03), the relative HR (Grp1 = 82%HRmax v Grp2 = 80%HRmax) and RPE (Grp1 = 11.5 v Grp2 = 11.2) were the same (p > .37)

Table 1. Practice v test walk pace and distance

	Practice distance walked (m)	6MWT distance (m)	Practice test pace (m.min ⁻¹)	6MWT pace (m.min ⁻¹)	95% LoA pace Practice v 6MWT (m.min ⁻¹)
Group 1 2 min practice	115 (27.7) <i>Equates to 345 [83.1] m/6 min</i>	329 (95.7)	57.5 (13.8)	54.9 (15.9) 4.5% < practice pace (NS)	12.1
Group 2 6 min practice	404 (93.7)	424 (81.4)	*67.3 (15.6)	*70.7 (13.6) 6% > practice pace (NS)	12.1

LoA = Limits of Agreement, *Significantly faster walking pace than Group 1 (p = .03)

Conclusions:

- Within each of the two groups, walking pace was not significantly different between the practice and the actual 6MWT. This was best confirmed by the same 95%LoA, between the practice and the actual test, being 12.1 m.min⁻¹
- Although the full 6-minute practice showed no sign of causing fatigue, this data provides good preliminary evidence that a 2-minute practice achieves the same purpose whilst saving valuable clinical assessment time
- Further data collection and analysis of the effects of a 2-minute versus 6-minute practice test on longer-term reliability (e.g. between beginning and end of programme) of the 6MWT is still required.

Appendix 14



Post-exercise Brain Natriuretic Peptide levels in chronic heart failure patients: a pilot study

R. Leslie^{1,2}, K. George FACSM³, J.P. Buckley²

¹Royal Wolverhampton NHS Trust, UK; ²University of Chester, UK; ³Liverpool John Moores University, UK

Abstract: Brain Natriuretic Peptide (BNP) is a marker of myocardial damage and reported to increase significantly following maximal exercise in patients with chronic heart failure (CHF). Little evidence however exists on BNP levels following standard and recommended submaximal exercise sessions for CHF. **Purpose:** This pilot study, as part of a larger study, aimed to assess changes to BNP levels immediately, and at 24, 48 and 72 hours following a recommended CHF exercise training session. **Methods:** Five participants (Table 1) with CHF, had venous blood samples taken at four time points following 20 to 30 mins continuous exercise at 40 – 60% of heart rate reserve (and/or Borg RPE 12-13). **Results:** summarised in Figure 1. **Conclusions:** No participant had an increase in BNP, either immediately or serially over three days, following exercise. These results provide preliminary evidence for exercising CHF participants in multiple weekly sessions without the need for recovery days to prevent accumulated rises in BNP. Data is currently being collected on larger numbers of participants to further substantiate these findings (Table 2).

Introduction: Brain or B-type Natriuretic Peptide (BNP) and its N-terminal propeptide (NT-proBNP) are markers of myocardial wall stress. Levels are reported to increase significantly following maximal exercise in patients with chronic heart failure (CHF). Little evidence however exists on BNP levels following standard and recommended submaximal exercise sessions for CHF.

Aims: This pilot study, as part of a larger study, aimed to assess changes to BNP levels immediately, and at 24, 48 and 72 hours following a recommended CHF exercise training session.

Methods: Five (4 males) NYHA Class II & III CHF patients (60% from coronary heart disease) were recruited. All were stable on optimal medical therapy ≥ 4 weeks.

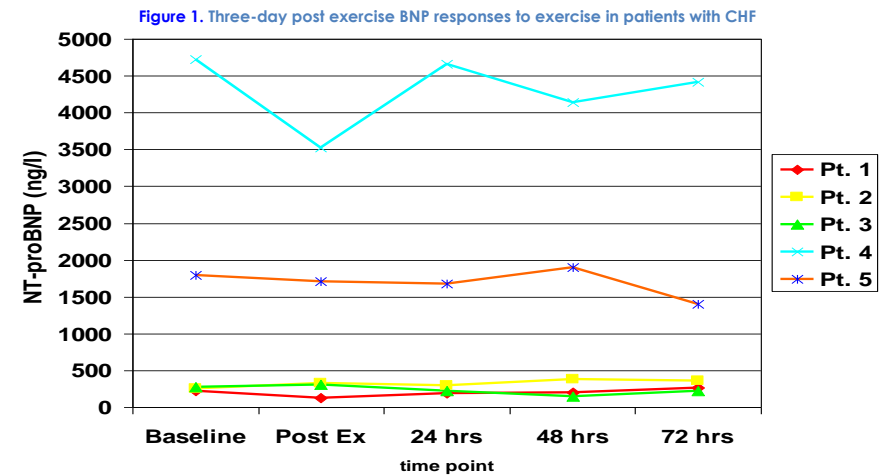
NT-proBNP levels measured via venous blood samples taken pre-exercise (baseline,) immediately post-exercise and again at 24, 48, and 72 hours post-exercise, at the same time of day.

Patients exercised at 40 – 60% heart rate reserve (HRR) and a rating of perceived exertion (RPE) of 12 -13 on the Borg Scale for 20 to 30 minutes.

Results: Baseline patient characteristics are summarised in Table 1. Figure 1 illustrates changes in NT-proBNP across the five time points, where there were no significant changes following the exercise session.

Table 1. Patient baseline characteristics

Age (years)	48 - 78
Male/female (n)	4/1
BMI (kg/m ²)	24.0 – 33.8 (mean 24.4 \pm 0.6)
CHF cause: Idiopathic/ischaemic (n)	2/3
LVEF (%)	30 - 44
NYHA class II/III (n)	3/2
6MWD (m)	325 - 585

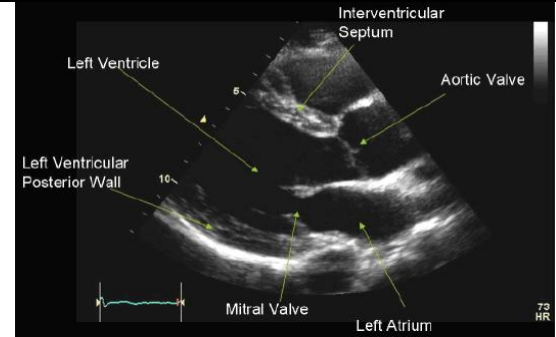
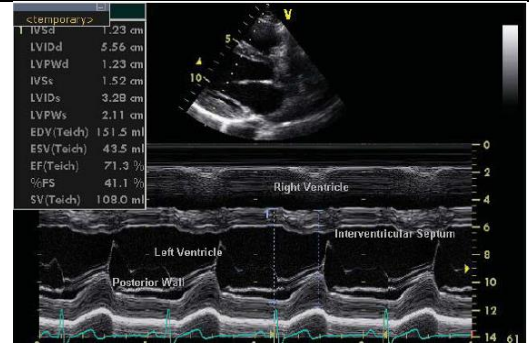


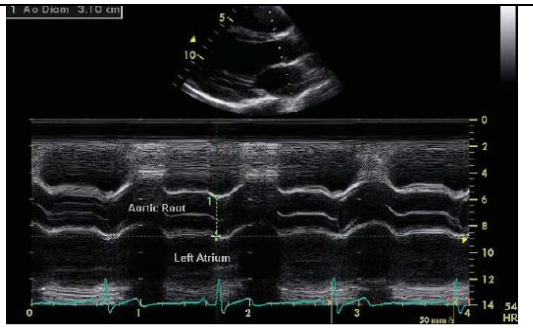
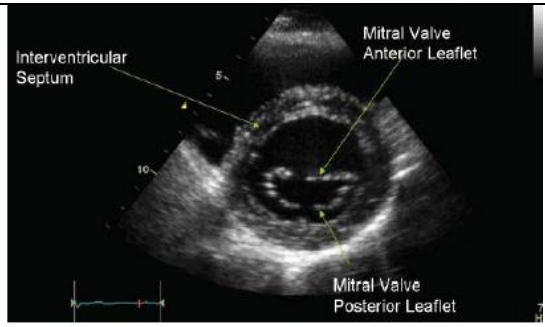
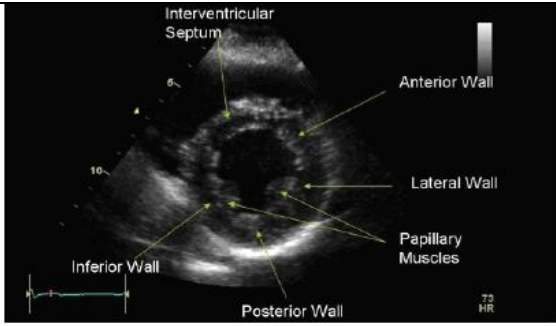
Summary and Conclusion: The results of this pilot study support the findings of several studies, which all reported only minor changes in plasma BNP levels following both moderate and maximal-intensity exercise in patients with CHF (Friedl et al., 1999; McNairy et al., 2002; Krüger et al., 2004; Normandin et al., 2013). Future studies are required to assess the possible mechanisms of why some studies report increases in BNP levels and others do not, which could include the evaluation of BNP clearance and/or the inability of the compromised ventricles to synthesize BNP relative to the demands of the system. These results provide preliminary evidence for exercising CHF participants in multiple weekly sessions without the need for recovery days to prevent accumulated rises in BNP.

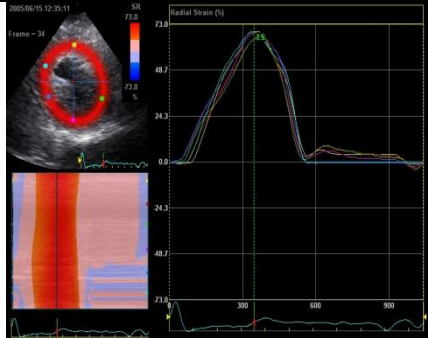
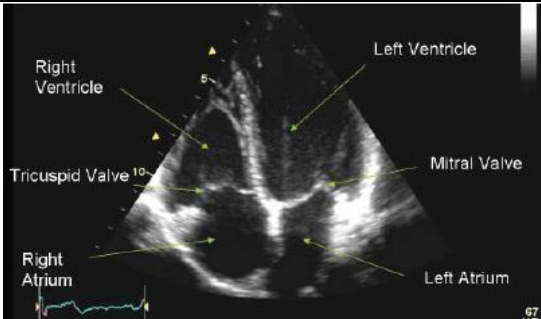
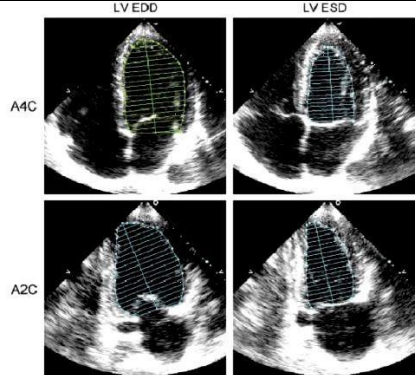
Table 2. Post-abstract submission results: Three-day post exercise BNP responses to exercise in patients with CHF (n = 16)

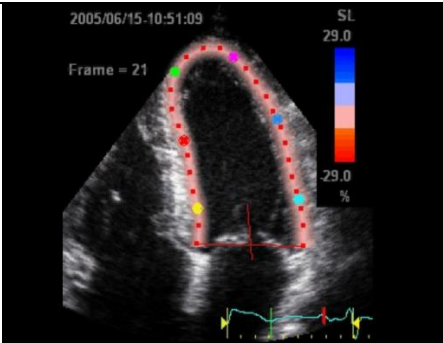
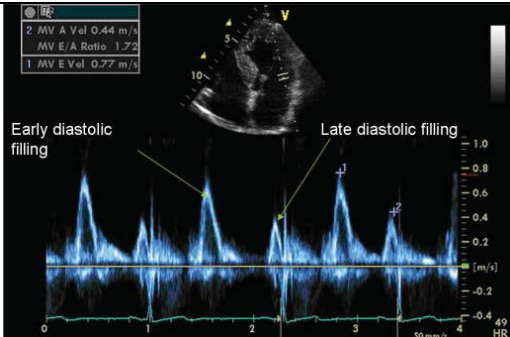
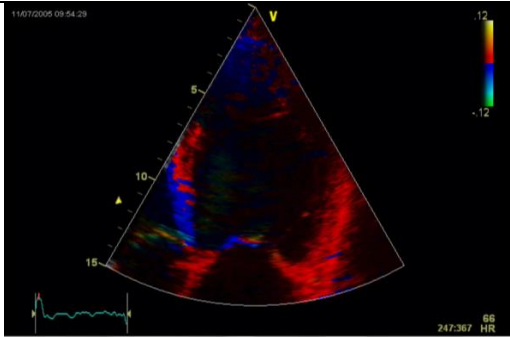
BMI (kg/m ²)	LVEF (%)	6MWD (m)	Baseline NT-proBNP (ng/l)	Post-exercise NT-proBNP (ng/l)	24 hrs NT-proBNP (ng/l)	48 hrs NT-proBNP (ng/l)	72 hrs NT-proBNP (ng/l)
27.5 \pm 3.5	33.44 \pm 7.4	403.4 \pm 94.2	1574.06 \pm 1848.716	1468.75 \pm 1544.204	1642.88 \pm 2148.246	1397.94 \pm 1598.986	1460.38 \pm 1567.834

Appendix 15

ACQUISITION	FPS	MODE	NOTES	OFFLINE MEASURES	SAVE	EXAMPLE
PLAX	40-90	2D	Parallel IVS and PW; MV centred in sector; adjust depth so that LV fills sector; focal point in line with valves	Using post-hoc M-Mode with angle correction for BOTH LV and LA (LVIDd, LVIDs, PWd, PWs, IVSD, IVSs, LAIDs)	CLIP	
PLAX	40-90	M-Mode (LV)	Align cursor to tips of MV, perpendicular to IVS and PW; adjust angle if required	LVIDd, LVIDs, PWd, PWs, IVSD, IVSs	IMAGE	

PLAX	40-90	M-Mode (Ao Root/LA)	Align cursor through Ao root and centre of LA	* all measures taken in systole	IMAGE	
PSAX – BASE	40-90	2D	Clear endo- and epi- definition, just below MV; no dropout throughout cycle	Myocardial Speckle tracking (circumferential, radial strain/strain rate; rotation)	CLIP	
PSAX – MID	40-90	2D	As above but at level of papillary muscles; increase depth and adjust sector width as needed; focus point in centre of cavity	Myocardial Speckle tracking (circumferential, radial strain/strain rate; rotation)	CLIP	

PSAX – APEX	40-90	2D	As above but just before LV obliteration; move down a rib space and laterally to maximise image acquisition	Myocardial Speckle tracking (circumferential, radial strain/strain rate; rotation; torsion)	CLIP	
A4C	40-90	2D	Whole image	LV and LA volume (biplane)	CLIP	
A4C (LV,LA only)	40-90	2D	Adjust depth to include LV, MV and LA only	LV, LA volume (biplane)	CLIP	

A4C (LV only)	40-90	2D	Focus on LV only; no wall dropout throughout cycle	Myocardial speckle tracking (longitudinal strain/strain rate)	CLIP	
A4C	40-90	PW DOPPLER	Overlay MV with colour to determine point of greatest flow, adjust sample volume to tips of MV	Transmitral E, A, E/A, other timing/flow measures	IMAGE	
A4C	>200	COLOUR TDI (TVI)	Narrow sector to increase FPS; adjust gain to reduce noise	Velocity, displacement, strain, strain rate	CLIP	

A4C (IVS only)	>200	COLOUR TDI (TVI)	Narrow sector to include IVS, at mitral annulus, only; adjust gain to reduce noise	Velocity, displacement, strain, strain rate	CLIP	
A4C (PW Only)	>200	COLOUR TDI (TVI)	Narrow sector to include lateral wall only; adjust gain to reduce noise	Velocity, displacement, strain, strain rate	CLIP	
A5C	40-90	PW DOPPLER	Position sample volume inside LV, at the mid-point between MV and LVOT	Timing, flow measures	IMAGE	
A2C (LV, LA only)	40-90	2D	Find A4C and rotate probe until A2C view; ensure clear definition of	LV, LA volume (biplane)	CLIP	

Appendix 16

Leslie R and Buckley JP. Low pulse pressure does not reduce the efficacy of a heart failure exercise programme. *British Journal of Cardiology* 2012; 19:30 –